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ORIGIN OF FETAL ADENOMA IN THE THYROID GLAND

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The term "fetal adenoma" has long occupied a place in the literature on the thyroid gland. The first use of this term is generally credited to Wölfler,[1] who in 1883 used it to designate certain nodular tumors of the thyroid gland, which he thought arose from fetal cell rests. With an advance in knowledge, however, the concept of a fetal origin for these nodules has largely been discarded, although through usage the term persists in the literature. Today it has come to designate a distinctive type of nodule, on the general features of which most observers are agreed.

While a detailed description of a typical "fetal adenoma" will be given later (fig. 1), a few of its distinctive features may be cited here. Such a nodule is discrete, circumscribed, encapsulated and of variable size, occurring alone or multiply and presenting to the unaided eye a dull gray homogeneous substance with no evidence of lobulation. Histologically, it is comprised of small groups of cells, with or without acini, that may have a uniform distribution or show a tendency to congregate toward the periphery of the nodule. The acini are embedded in a homogeneous, eosinophilic, acellular matrix, not unlike colloid in its staining reactions, which is characteristically lacking in connective tissue. The nodule usually has a rich capillary blood supply.

Wölfler noted the occurrence of circumscribed areas in the thyroid gland "varying in size from that of the head of a pin to that of a goose egg." Variations in color and consistency were noted. Some glands contained more than one "adenoma." Microscopically, the smaller nodules were "formed of nonorganized gland cell tissue" and

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1. Wölfler, A.: Ueber die Entwickelung und den Bau des Kropfes, Arch. f. klin. Chir. **29**:1-97, 1883.

"looked like the embryonic thyroid." In his material it was rare to find the "formation of large vesicles or extensive colloid degeneration." Without knowing the etiology and pathogenesis of an adenoma of the thyroid gland, he stated "with some sureness that they are of congenital nature," and more specifically, that they arise from interacinar cell rests. He further added that "these adenomas have a perceptible size at time of birth" or that "they develop at the time of puberty or pregnancy out of congenital structures."

Wölfler's concepts as recorded by his descriptions and diagrams have some features which suggest that he was dealing with nodules of different types and even with true benign neoplasms. Technical improvements in the microscopic examination of tissues, notably examination of whole glands and serial sections, have disclosed certain erroneous deductions in the investigations of earlier workers. The uncertainty of Wölfler's observations and their interpretation makes appraisal of his views impracticable. Nevertheless, he represents the school which originally sponsored the fetal origin of this condition.

Beck,[2] even earlier than Wölfler, attributed a fetal origin to adenomas of the thyroid gland. Ribbert[3] in 1915 resurrected the same belief. One cannot be certain, however, whether he had in mind the "fetal adenoma" exclusively or the comparatively rare true benign neoplasm, or even both types of lesions. While adhering to the fetal origin of the adenoma, he suggested a different mechanism for its formation. He described isolated cell groups in the form of solid epithelial bodies, lying between alveoli that did not possess lumens and were surrounded by a thin layer of connective tissue. Generally not more than two such bodies could be found in a single gland. Ribbert expressed the belief that these were not formed at puberty or when the adenoma first became visible, but that their occurrence must be attributed to rests of embryonal epithelium which did not form alveoli with lumens but continued to form solid cell masses. Thus, while Ribbert's description would indicate that he was considering a true benign neoplasm, his opinions, nevertheless, have become associated with those having to do with the so-called fetal adenoma and the embryonal origin thereof.

Virchow,[4] Hitzig[5] and Michaud[6] represent the school of earlier writers who explained the formation of an adenomatous nodule in the

2. Beck, B.: Ueber eingesackten Drüsengewebe-Kropf, Arch. f. physiol. Heilk. **8**:136-138, 1849.

3. Ribbert, H.: Das Adenom der Schilddrüse, Frankfurt. Ztschr. f. Path. **18**: 55-56, 1915.

4. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 3, no. 1, pp. 15-17.

5. Hitzig, T.: Beiträge zur Histologie und Histogenese der Struma, Arch. f. klin. Chir. **47**:464-502, 1894.

6. Michaud, L.: Die Histogenese der Struma nodosa, Virchows Arch. f. path. Anat. **186**:423-477, 1906.

thyroid gland on a basis other than origin from fetal cell rests. Virchow, writing on pathologic tumors in 1863, discussed the process of hypertrophy and of hyperplasia and pointed out that each, at times, is a manifestation of normal growth. By a process of budding in certain parts of the follicles, he explained that small solid cones of cells push themselves into the interstitial tissues and, because of an increase in the latter, become isolated as discrete growths, which eventually acquire a fluid-containing lumen. This process, which he believed to be the fundamental one in the formation of goiter, may be diffuse or focal. He attributed the occurrence of an adenomatous nodule to secondary inflammatory changes.

Hitzig expressed the belief that a nodular goiter begins as a single area of differentiated epithelium, which, by a process of metaplasia, gradually replaces the normal tissue of a lobule or even of a lobe. This process, he explained, is essentially due to a difference in the growth potential of neighboring parts of the gland.

Michaud summarized the beliefs of this group when he said: "We believe as Virchow that a goiter nodule develops out of normal epithelium, with Hitzig's modification that it is simply a substitution of normal thyroid tissue by changed cells which arise from the normal tissue."

In considering the present day concepts of the "fetal adenoma," we find less unanimity of opinion as to its nature than existed among the early writers. On only one point does there seem to be any general agreement, and that is that the lesion is not fetal in origin. While most writers recognize it as an interesting histologic entity, its pathogenesis has not generally been elaborated on. Some positive views have been expressed, which are given here.

Rienhoff and Lewis,[7] in their discussion of benign tumors, expressed the belief that the term "fetal adenoma" is a misnomer and should be discarded because of insufficient evidence to support the theory of origin from interacinar embryonal cell rests. However, in discussing the hyperplasia-involution cycle, they pointed out that certain glands may undergo an extreme degree of hyperinvolution and that this same type of extreme involutional change is also to be found in the so-called fetal and mixed adenoma.

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7. Rienhoff, W. F., and Lewis, Dean: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16**:79-116 (Jan.) 1928. Rienhoff, W. F.: Involutional or Regressive Changes in Thyroid Gland in Exophthalmic Goiter, and Their Relation to Origin of So-Called Adenomas, ibid. **13**:391-425 (Sept.) 1926. Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1935.

Boyd [8] stated that many of the nodules which have been regarded as fetal in type are essentially only varieties of the colloid adenoma, since both may be seen shading into the other in the same sections. He noted further three special features about the "fetal adenoma," namely, (1) numerous thin-walled dilated vascular channels, (2) frequent extensive hemorrhages and (3) active budding of the acini within the adenoma. In addition there are a small number of adenomas which have the characteristics of a neoplasm and possibly arise from fetal cells. These are composed of strands of solid clusters of cells with no lumens, supported in a delicate vascular stroma.

MacCallum [9] rejected the term "fetal adenoma" and considered this lesion as a type of nodular goiter, arising from adult cells and frequently occurring in company with colloid nodules.

Wegelin [10] expressed the belief that the "fetal adenoma" arises in later life from thyroid tissue and is not fetal in origin.

Williamson and Pearse [11] stated that the fetal adenoma is a manifestation of a retrogressive phenomenon, attributable to perilobar fibrosis.

Hertzler [12] expressed the belief that the nodule begins as a mass of thyroid tissue which has never reached an adult stage and that it shows malignant tendencies and should be looked on as a true neoplasm.

Kline [13] cited evidence to support the belief that the development of all forms of adenomatous goiter depends essentially on an irregularity in the degree of proliferation of acini in different portions of the gland.

Else,[14] writing on "Adenomatosis or the Diffuse Adenomatous Goiter," described what he regarded as a clinicopathologic entity characterized by a diffuse new formation of acini, usually involving the entire thyroid gland. In the beginning the growth is of the fetal type without secretion, but later it progresses to the adult type; it does not give rise to symptoms at first, but later signs of hyperthyroidism appear. On studying the pathogenesis of this condition he found masses of

8. Boyd, William: Surgical Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1933.

9. MacCallum, W. G.: A Textbook of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

10. Wegelin, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 1.

11. Williamson, G. S., and Pearse, I. H.: The Pathological Classification of Goitre, J. Path. & Bact. **28**:361-387, 1925.

12. Hertzler, A. E.: Mixed Tumors of Thyroid Gland (Fetal Adenomas), Arch. Surg. **16**:1187-1200 (June) 1928.

13. Kline, B. S.: The Origin of Adenomatous Goiter, Am. J. Path. **1**:235-239, 1925.

14. Else, J. E.: Adenomatosis, or the Diffuse Adenomatous Goiter, J. A. M. A. **85**:1878-1882 (Dec. 12) 1925.

undifferentiated cells, from which arose acini of the fetal type, followed in turn by the formation of a more adult type of colloid-secreting acinus. Different rates of development in various parts of the gland gave the nodular effect, and encapsulation was poor. As to the origin of these new acini, he favored the view that they arise from interstitial cells but also suggested that they may develop from the cells lining the old acini but growing "outside" the walls of these acini. Wilson [15] in 1913 described a similar condition and applied the term "adenomatosis." Goetsch [16] in 1920 described the early stage of this growth, applied the term "diffuse adenomatosis" and regarded the formation of acini as "an abortive attempt at the formation of young small alveoli."

Marine and Lenhart [17] regarded the "fetal adenoma" as a benign tumor which shows wide variations in its histologic picture, particularly in regard to the amount of colloid present and the height of the epithelium. They expressed the belief that it has a period of active growth and a resting period, comparable to physiologic hyperplasia, and, further, that iodine produces no change in the colloid.

HISTOLOGIC DESCRIPTION

The purpose of this paper is to show what we believe to be the origin of "fetal adenoma." This formation is identified by its specific histologic structure, and for clarity we have chosen a typical example for description (figs. 1 to 3).

Under low power magnification, section of such a growth shows a discrete, ovoid nodule, measuring about 4 cm. in its longest diameter and bordered by a thin capsule. This capsule is composed of strands of fibrous connective tissue, enmeshed in which are compressed thyroid follicles lined by atrophic epithelium. A few lymphocytes are present in the interstitial tissue. At irregular intervals the capsule sends fibrous strands into the substance of the nodule for short distances, usually accompanied by blood vessels. The central portion of the nodule is devoid of fibrous tissue.

The supporting framework is a loose reticulum, enmeshed in which is a pale, homogeneous, eosinophilic, acellular matrix. This material resembles intra-acinar colloid in sections stained with hematoxylin and eosin, and it displays the staining reaction of colloid in sections stained by Unna's method.

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15. Wilson, L. B.: The Pathology of the Thyroid Gland in Exophthalmic Goiter, Am. J. M. Sc. **146**:781-790, 1913.

16. Goetsch, E.: Disorders of the Thyroid Gland, Endocrinology **4**:389-402, 1920.

17. Marine, D., and Lenhart, C. H.: The Pathological Anatomy of the Human Thyroid Gland, Arch. Int. Med. **7**:506-536 (April) 1911.

The follicles are most abundant at the periphery, and the adjacent capsule is intimately attached. Toward the center of the nodule the follicles become less numerous but otherwise appear to be similar to those at the periphery. The follicles are uniformly small and round and contain little or no colloid; when present, the colloid is pale and vacuolated. The individual cells are uniformly large and high cuboidal and contain abundant cytoplasm, in which granules and vacuoles are seen. The nuclei are large and deeply basophilic, and many show one or more nucleoli. Histologically, these cells appear to be active. In the central, less dense areas, the follicles assume a chainlike configuration, with from three to eight small follicles lying in a row. In some

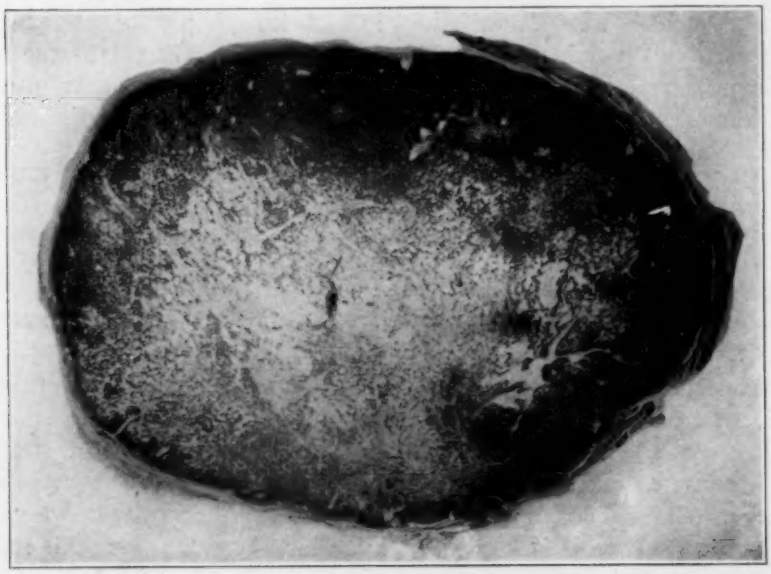

Fig. 1.—Low power photomicrograph of a typical fetal adenoma. Note the capsule and the peripheral concentration of acini.

of these chains a contiguous lumen may be detected. This suggests the formation of new follicles by a process of budding, similar to that which is known to occur in the development of the fetal thyroid. This same chainlike configuration is seen near the periphery, but it is not as apparent there as in the less dense areas.

The nodule is well vascularized throughout. In the capsule, numerous large blood vessels are seen entering the periphery of the nodule. At these points there is a moderate amount of perivascular connective tissue, which appears to be carried in from the capsule. Within the nodule the tissue is even more richly vascularized, the vessels appearing

Fig. 2.—Medium power photomicrographs of the fetal adenoma in figure 1, showing the periphery and the central portion of the nodule. Note the dilated endothelium-bound spaces in the center.

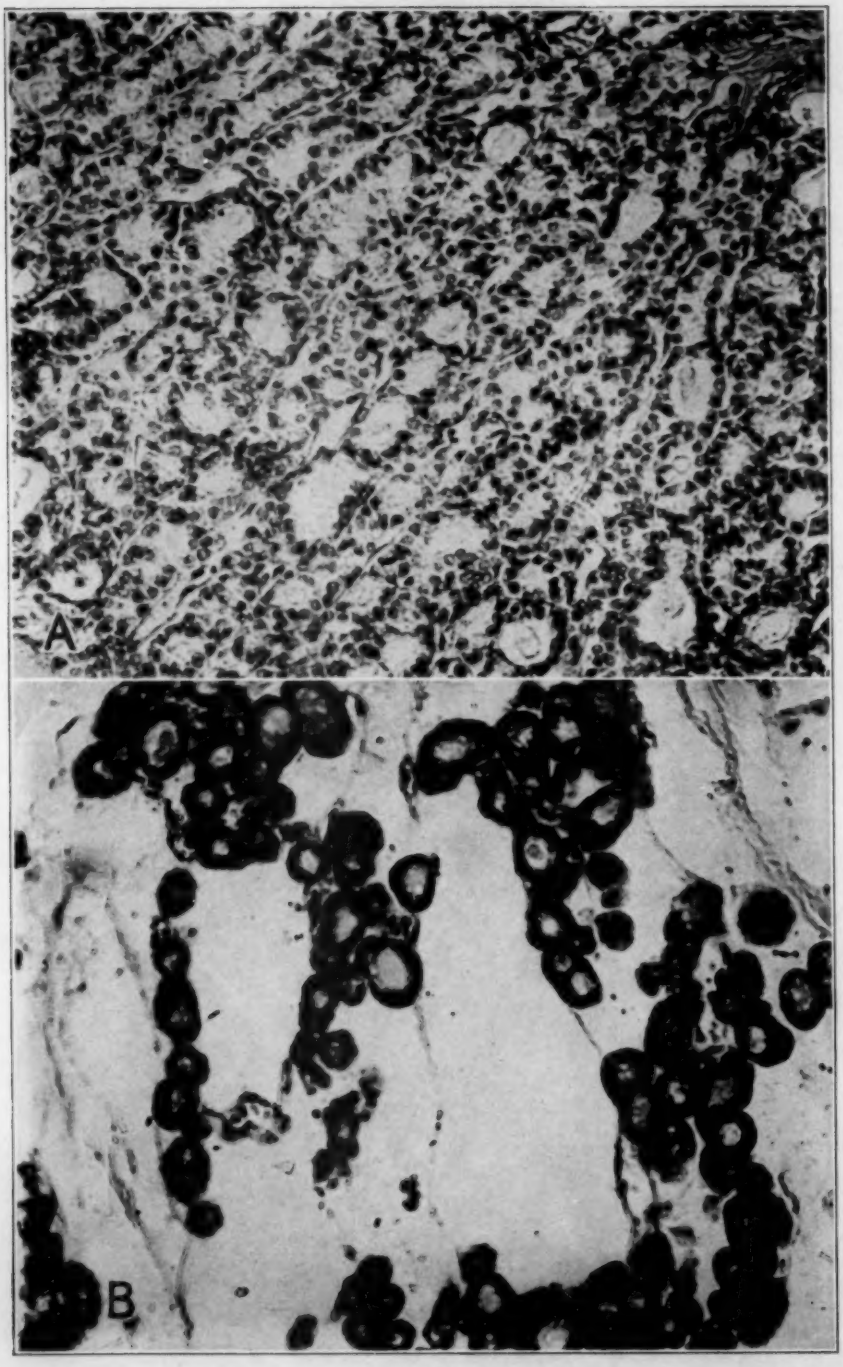

Fig. 3.—Photomicrographs showing the detailed histologic structure at the periphery and in the center of the nodule. Note that the epithelium in the center appears as active as that near the periphery.

merely as endothelium-lined spaces lying adjacent to closely packed acini. Near the center these vessels become markedly dilated and possess little or no supporting tissue.

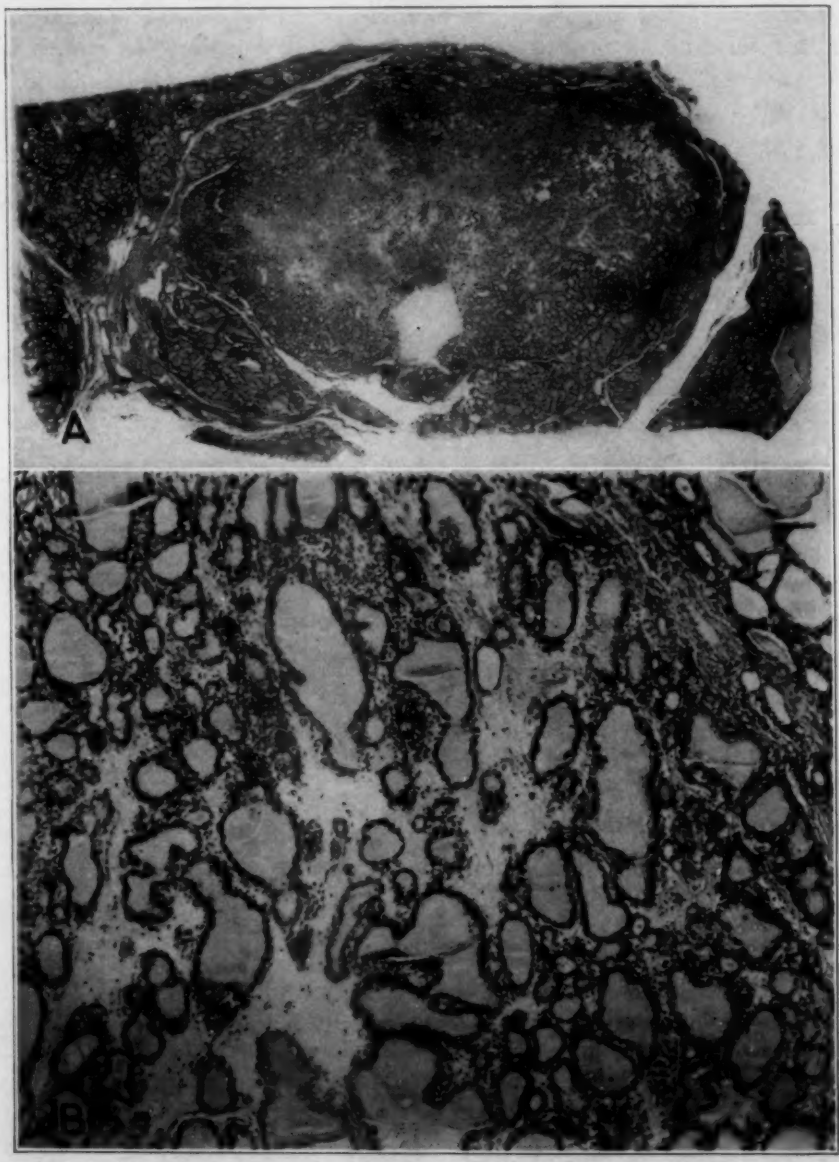

Fig. 4.—*A*, section of a fetal adenoma showing the peripheral acini undergoing hyperplasia and colloid deposition. *B*, high power magnification of the peripheral zone shown in *A*.

Noteworthy features in the foregoing description are (figs. 1 and 3): (1) small acini composed of normal adult thyroid cells; (2) absence of supporting connective tissue; (3) presence of numerous large endothelium-lined spaces, and (4) an acellular colloid-like matrix.

The individual components, acini, blood vessels and interacinar tissue, in this lesion are not characteristic of this particular nodule. It is rather the peculiar pattern they assume which gives the characteristic picture.

We have frequently seen nodules which present the typical appearance of a "fetal adenoma" near the center, while at the periphery they show larger acini composed of normal thyroid cells which are filled

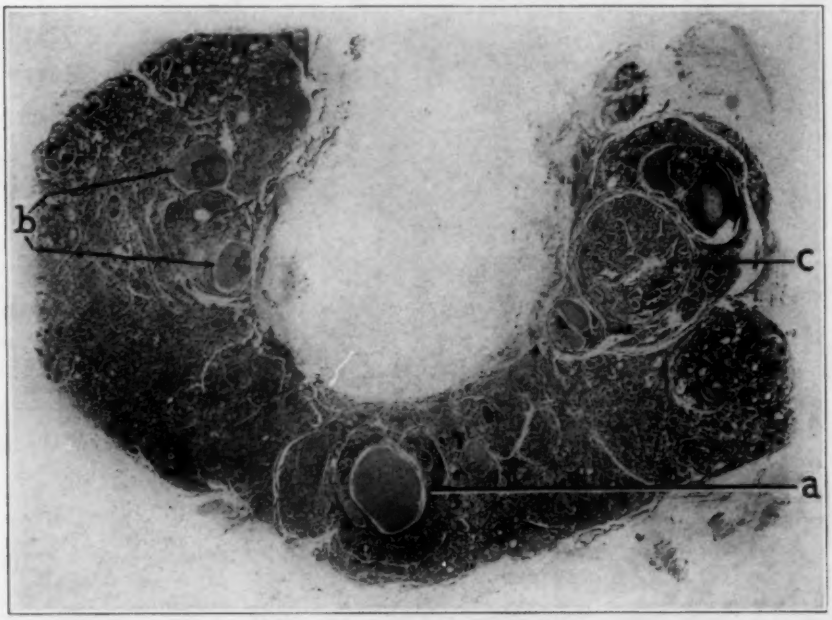

Fig. 5.—A transverse section through the whole gland, showing (*a*) a colloid body, (*b*) several colloid bodies into which papilliferous hyperplasia is taking place and (*c*) a nodule presenting the fetal pattern.

with colloid. In some instances these acini undergo hyperplasia, apparently reacting similarly to the remainder of the gland (fig. 4). On the other hand, we have seen this same picture as focal areas in a nonnodular gland. These changes have been repeatedly observed in routine autopsy material as well as in surgical specimens.

The "fetal adenoma" appears to consist of active thyroid cells, capable of undergoing the same histologic changes as those in a normal gland. We believe that the arrangement of the acini and not the acinus is the typical feature of the "fetal adenoma." This arrangement we

have termed the "fetal pattern." The next step is to show the method of formation of this pattern.

Figure 5 shows a transverse section through both lobes and the isthmus of a thyroid gland removed at autopsy from a 29 year old Negress, who was seven months pregnant, had a 4+ Wassermann reaction and after intravenous injection of thiobismuth collapsed and died in twenty-four hours. There were no apparent signs of hyperthyroidism.

Fig. 6.—High power magnification of the colloid body in figure 5.

On macroscopic examination of the gland on section, about six or eight discrete areas were seen scattered through the gland, giving it a nodular appearance. Microscopically, these areas may be classified in three groups, namely, (*a*) a single large colloid body, (*b*) several colloid bodies within which a papilliferous type of hyperplasia was taking place and (*c*) a large nodule which was almost completely filled by hyperplastic epithelium. The remainder of the gland showed a normal lobular configuration together with manifestations of diffuse hyperplasia.

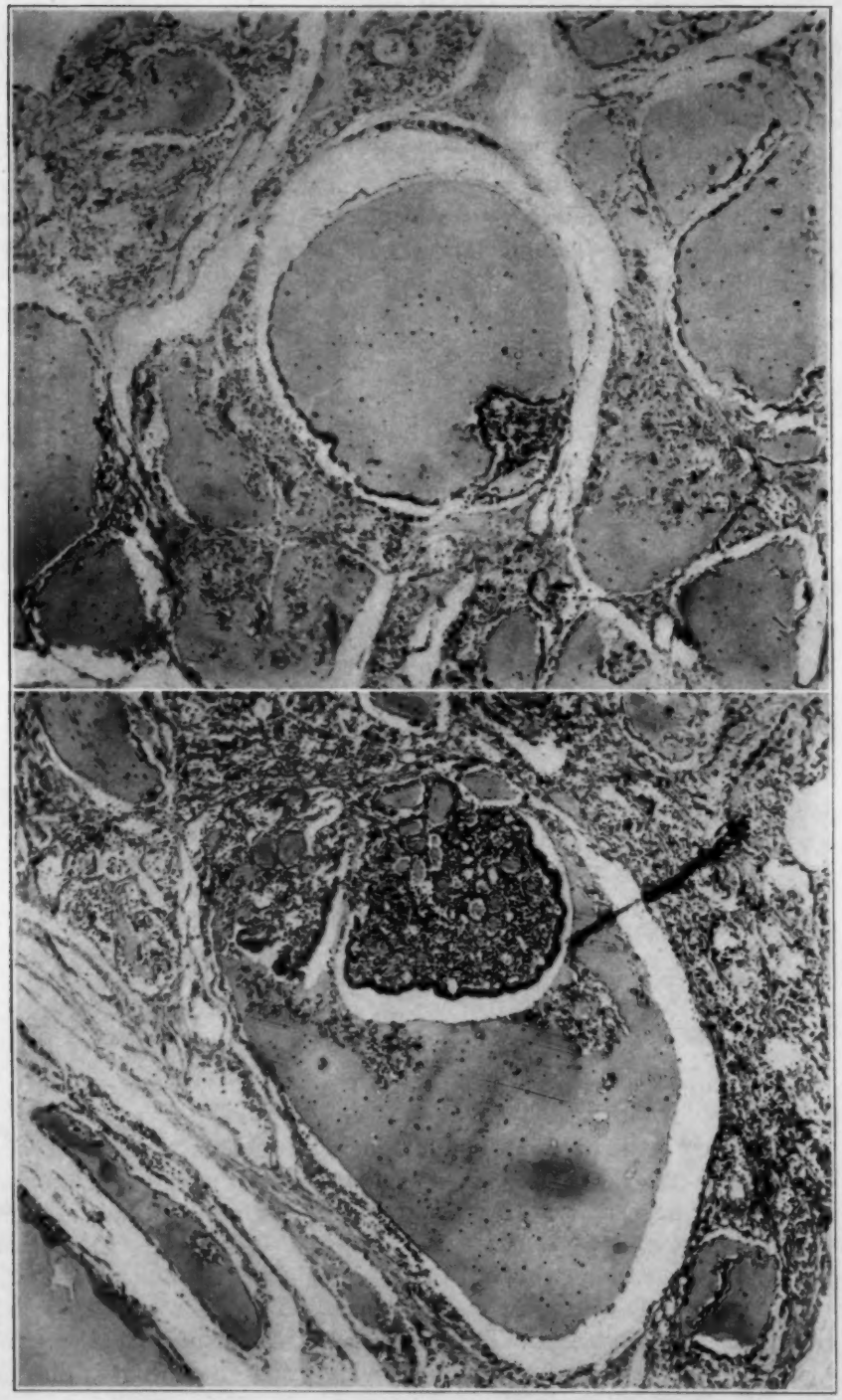

Fig. 7.—Papilliferous hyperplasia into the colloid bodies shown in figure 5*b*. Note the progressive stages of development as shown in these sections and in those in figure 8.

Fig. 8.—Further stages of papilliferous hyperplasia into the colloid bodies.

The single large colloid body (fig. 6), the position of which is shown in figure 5 *a*, was about 0.5 cm. in diameter. It was filled with deep-staining homogeneous colloid. The lining was composed of a single row of flattened epithelium. A pseudocapsule composed of a few loose strands of connective tissue surrounded the follicle.

The colloid bodies in the second group (figs. 7, 8 and 9) varied in size from 0.2 to 0.5 cm. in diameter and were filled with deep-staining, nonvacuolated colloid. One side of the follicle was lined by compressed,

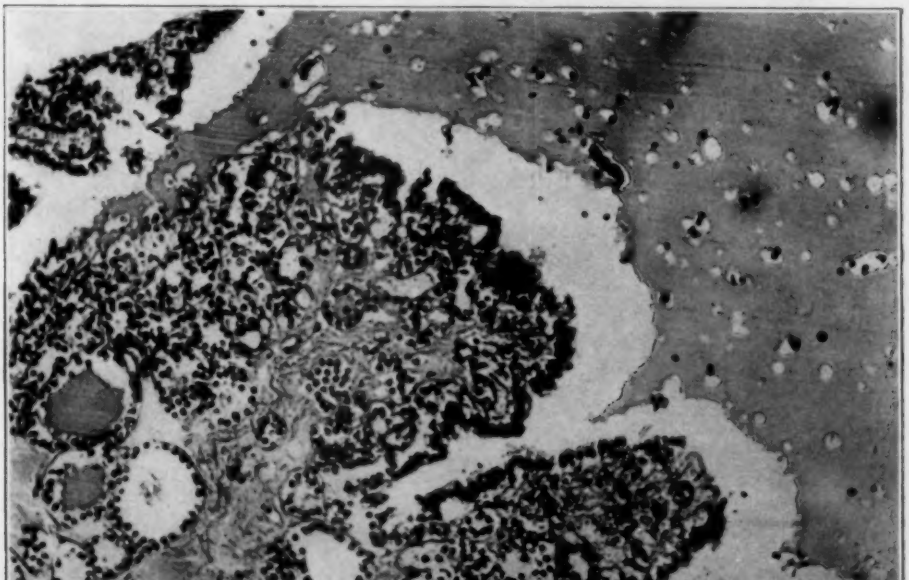

Fig. 9.—High power magnification of the section in figure 8 *B*, showing the typical fetal pattern.

flattened epithelium, while at the opposite side the epithelium was hyperplastic, manifesting itself as a papilliferous type of growth composed of finger-like and clublike projections into the colloid (fig. 9). As this tortuous epithelial wall advanced, it left behind it a matrix of colloid in which were formed numerous small follicles lined with hyperplastic epithelium, which were seen in all stages of development, as they were "pinched" or "budded" by a process of invagination of the epithelial lining. These cells were large and high cuboidal and

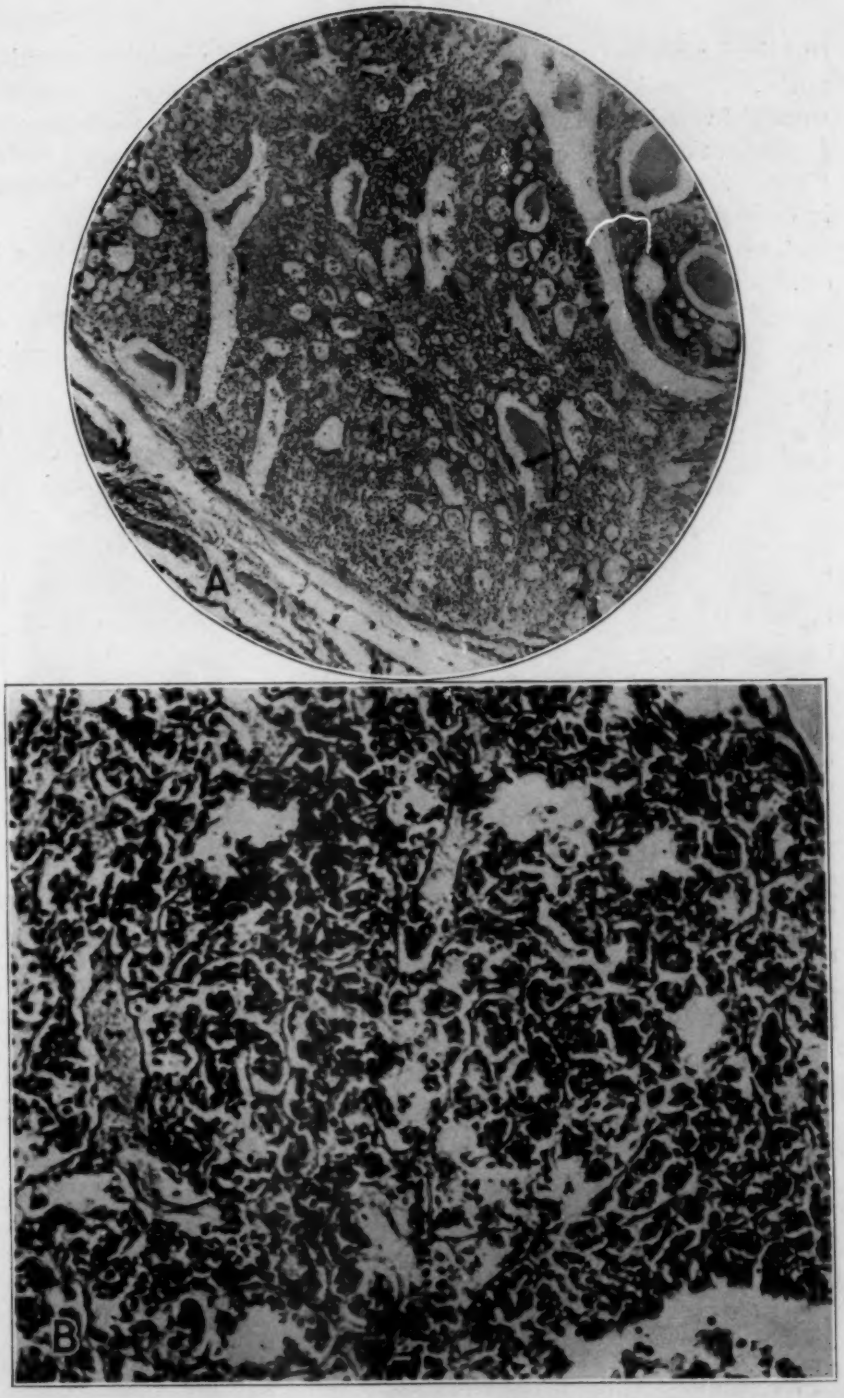

Fig. 10.—*A*, photomicrograph of a solid nodule. Note the similarity to the section in figure 2 *A*. *B*, high power magnification of *A*, showing details of the fetal pattern. Note the similarity of the sections in figures 3 *A* and 10 *B*.

contained abundant pale cytoplasm and large deeply staining granular nuclei. These hyperplastic areas were well vascularized. Numerous engorged vessels lying in close association with the follicles were present. In places, these blood channels might be seen invading the colloid itself. Figures 7 and 8 show the lesion in progressive stages of development in different nodules in the same section.

The large, apparently solid nodule (fig. 5 *c* and fig. 10) was about 1 cm. in diameter. It was surrounded by a narrow zone of loose connective tissue. Its structure was essentially the same as that of the hyperplastic zone found in the colloid bodies just described, the only noteworthy

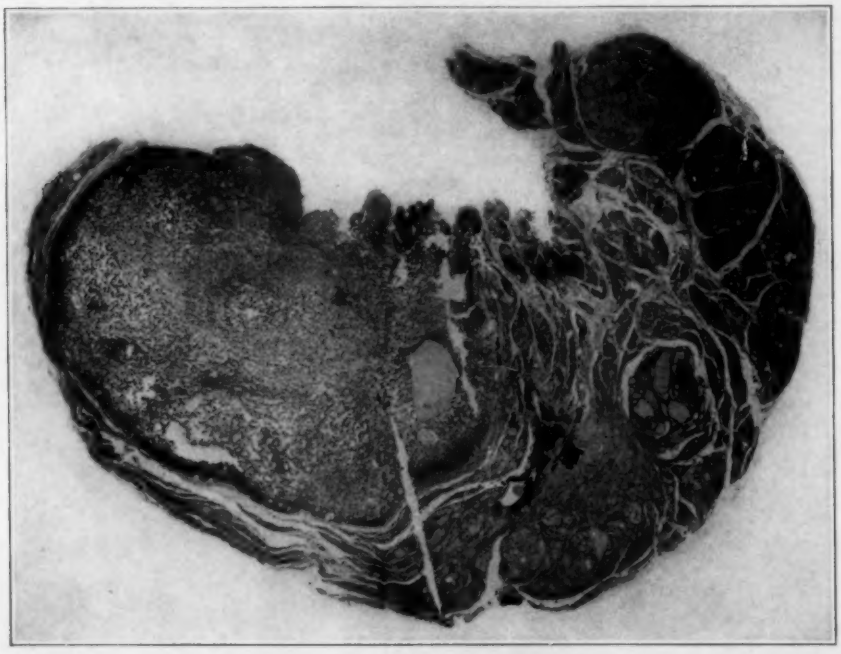

Fig. 11.—A large section through the entire lobe of a thyroid gland, showing a nodule of the fetal type.

difference being that here no colloid was present, the entire nodule consisting of small hyperplastic follicles. The character of the epithelium was identical with that previously described, and the same degree of vascularization was present (fig. 10 *B*). This nodule presented the typical fetal pattern described in figure 3 *A*.

The remainder of the gland showed evidence of hyperplasia of the intravesicular type.

We believe that the nodules described were originally colloid bodies. Hyperplasia of the epithelium occurred throughout the gland (a case of pregnancy), and the epithelial lining of the nodules became hyper-

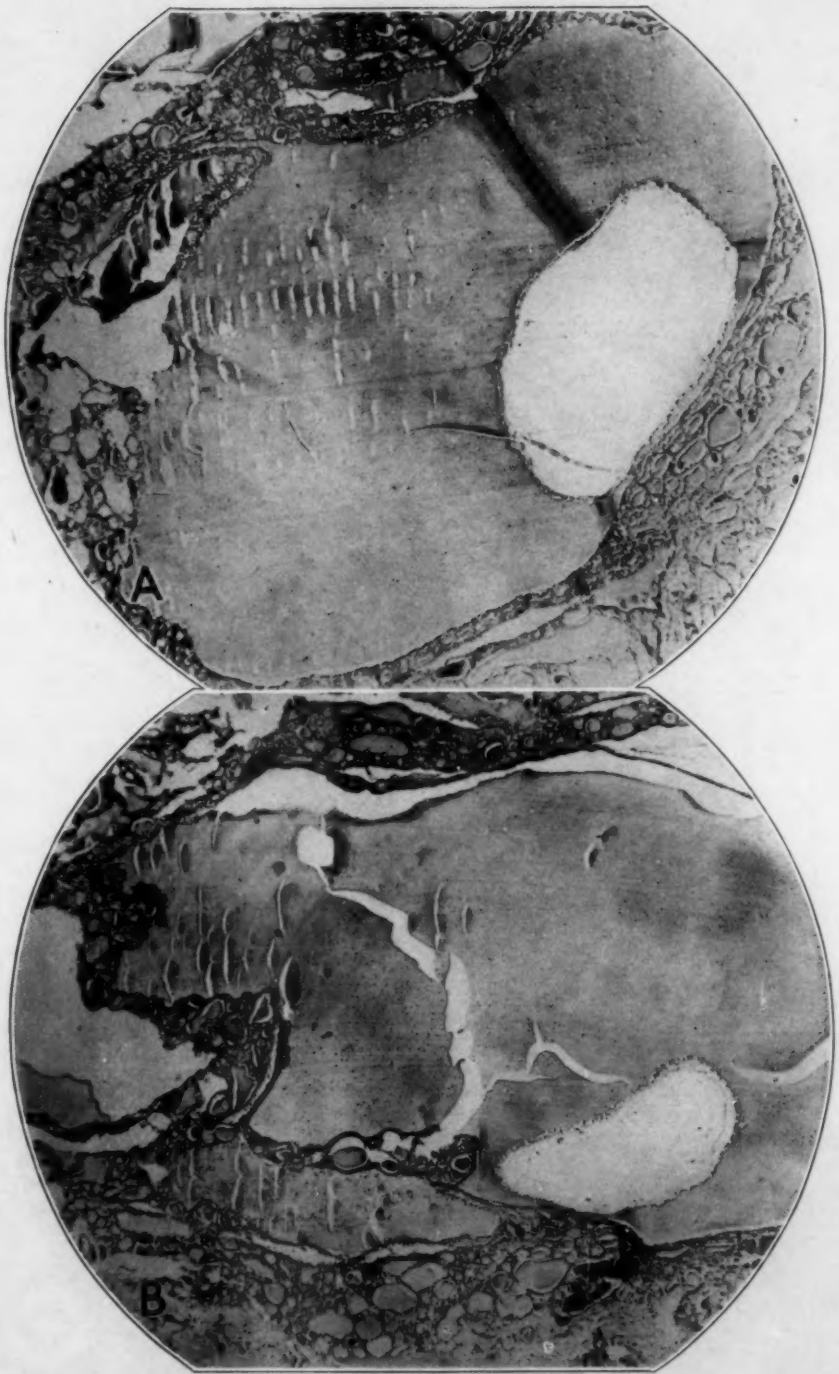

Fig. 12.—Section through the colloid body showing beginning hyperplasia at one border. Figures 12 to 15 are serial sections taken at 100 micron intervals through the same lesion.

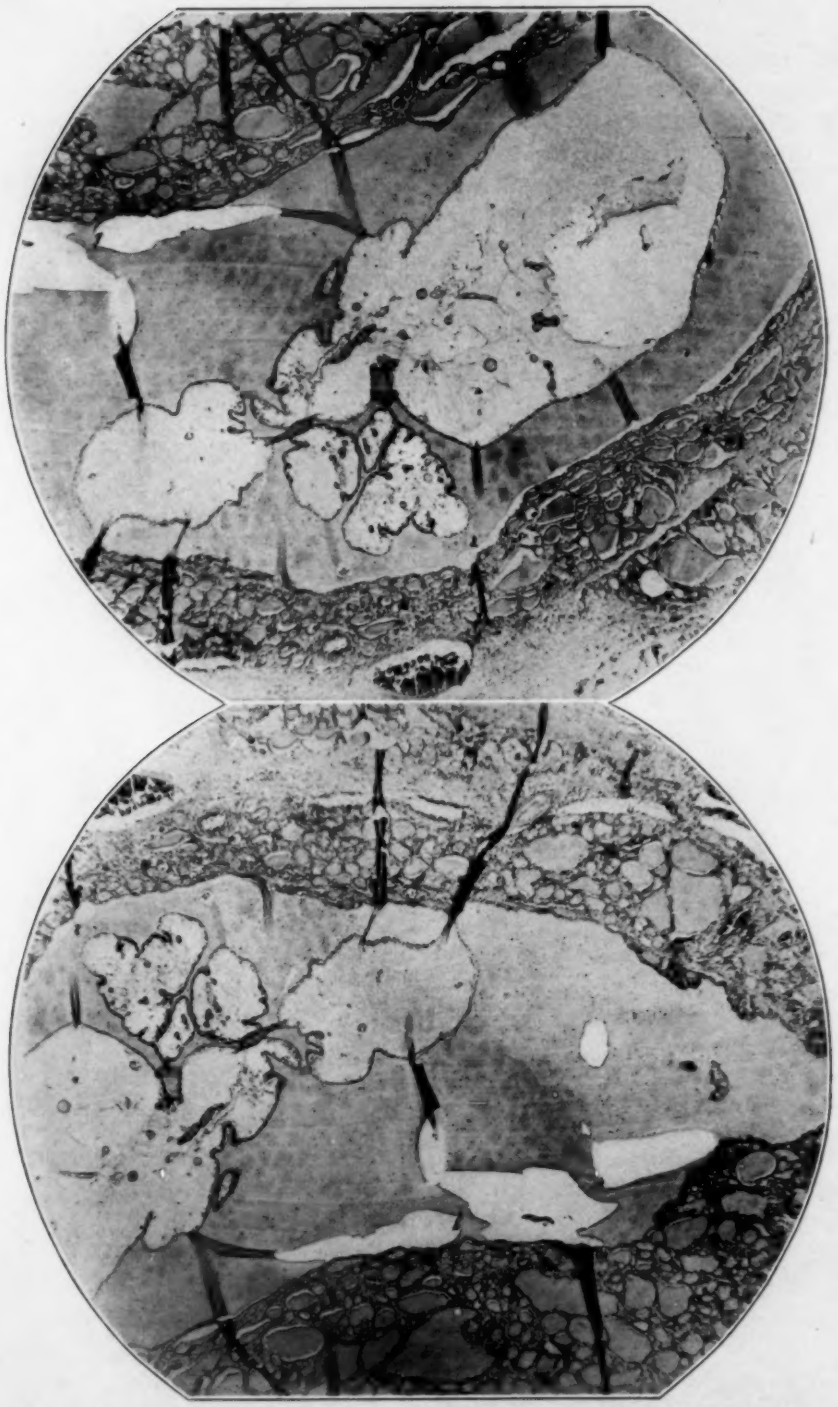

Fig. 13.—Section showing hyperplastic epithelium well advanced into the colloid body.

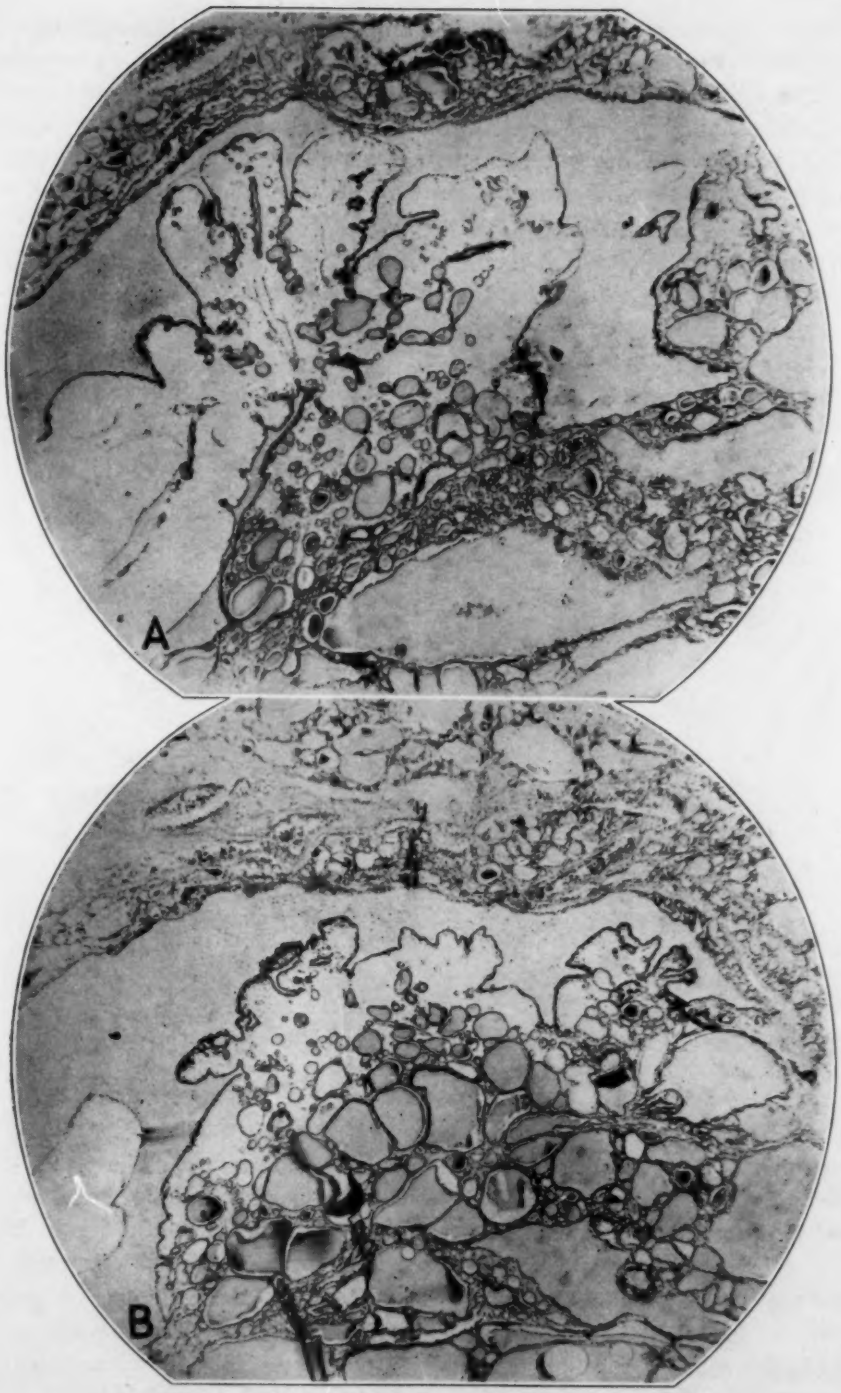

Fig. 14.—Further stages in the papilliferous ingrowth.

plastic, growing into the colloid. Three stages in the process were evident: (1) an unaltered colloid nodule, (2) the projection of hyperplastic epithelium into the colloid and (3) finally, complete replacement of the colloid by hyperplastic epithelial acini, arranged in the typical fetal pattern. In our routine surgical material this process has been frequently observed both in nodular and in non-nodular glands.

Figure 11 shows a section through the entire lobe of a gland, removed surgically, which to the naked eye presented the features of

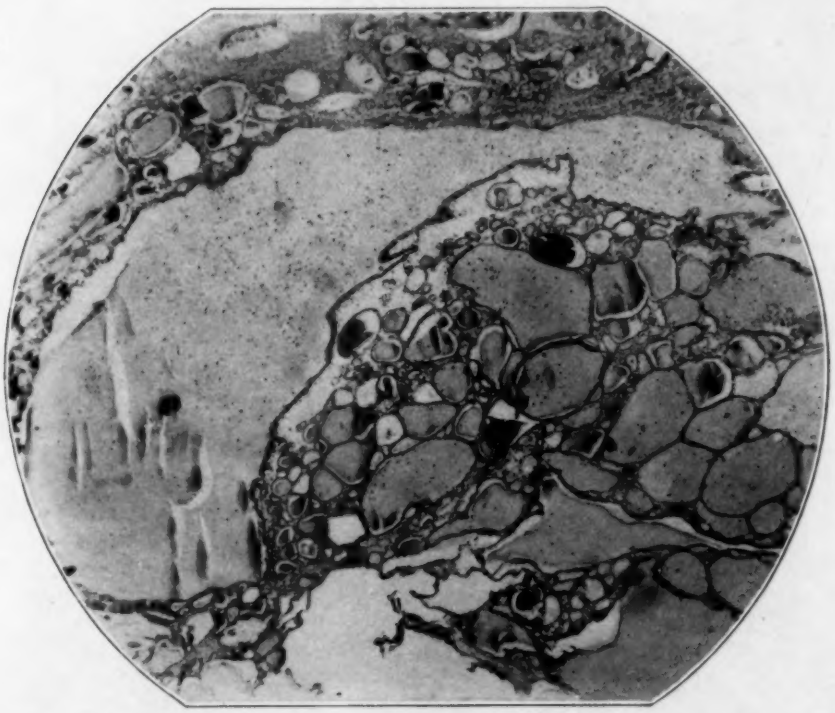

Fig. 15.—Section taken through the colloid body beyond the papilliferous ingrowth.

a nodular goiter containing one large and one small nodule. A large section was made, and the remainder of the gland was cut serially. Section through the larger nodule revealed that it was a fetal adenoma, similar in all essential features to the growth described in figure 1. The small nodule showed a focal area of hyperplastic epithelium, which had undergone moderate involution. The remainder of the gland showed evidence of a residual hyperplasia of a similar type.

Serial sections through non-nodular portions of the gland revealed processes similar to those just described (figs. 12, 13, 14 and 15).

Taking a section at random, for example, that shown in figure 14 *B*, there was to be seen a large irregular colloid body filled with vacuolated colloid. On one side there was a border of flattened epithelium, while on the other side the epithelium was high cuboidal and hyperplastic, causing the outline of the colloid to be irregular, owing to the finger-like and clublike projections which the advancing wall of hyperplastic epithelium sent into the colloid. In the wake of or behind this epithelial wall there was a matrix of pale, eosinophilic, acellular material in which

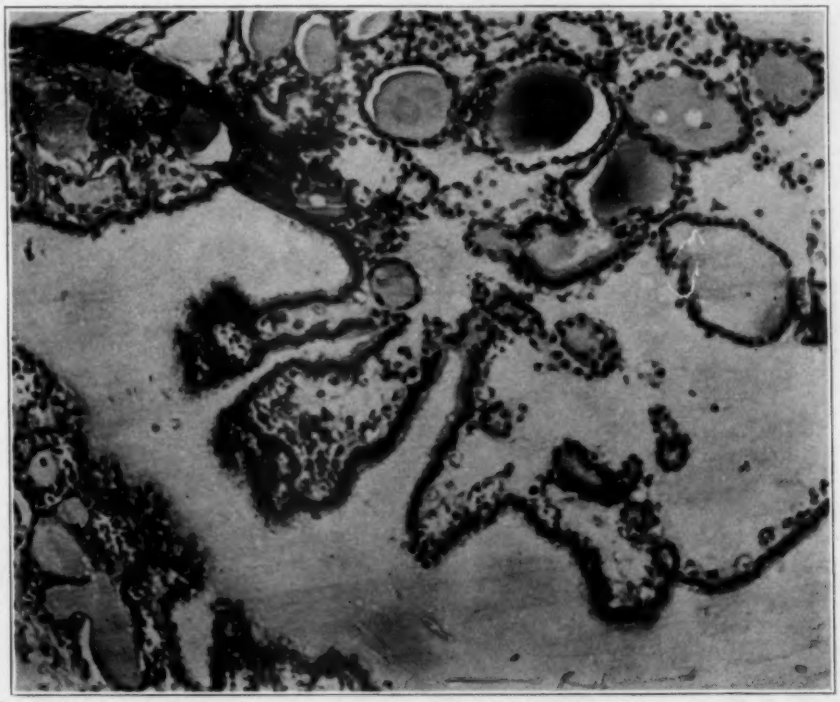

Fig. 16.—High power magnification of figure 14 *B*, showing marked hyperplasia with new acini in the process of formation.

were found numerous small follicles lined with hypertrophic epithelium and containing deep-staining colloid. Some of these follicles could be seen in the process of formation, as they were "pinched" or "budded" off from the epithelium. This area was well vascularized, numerous small vessels lying in close relationship to the epithelium of the follicles. By serial section the lesion was seen to be a colloid body (fig. 12 *A*) in which a papilliferous type of hyperplasia had occurred (figs. 12 *B* to 16), partially replacing the colloid and reproducing the fetal pattern. Similar areas were noted elsewhere throughout the gland.

In this type of hyperplasia the epithelium carries its blood supply with it, but in this variety of growth apparently the reaction occurs within an epithelium-lined space, and because the colloid gives temporary support to the invading epithelium, no proliferation of fibrous tissue occurs.

The appearance of the nodule depends on the size and on the secondary changes which may occur in it. If the original nodule is small, complete replacement by closely packed acini occurs (fig. 10 *A*), whereas in the larger lesions the replacement is incomplete, the acini

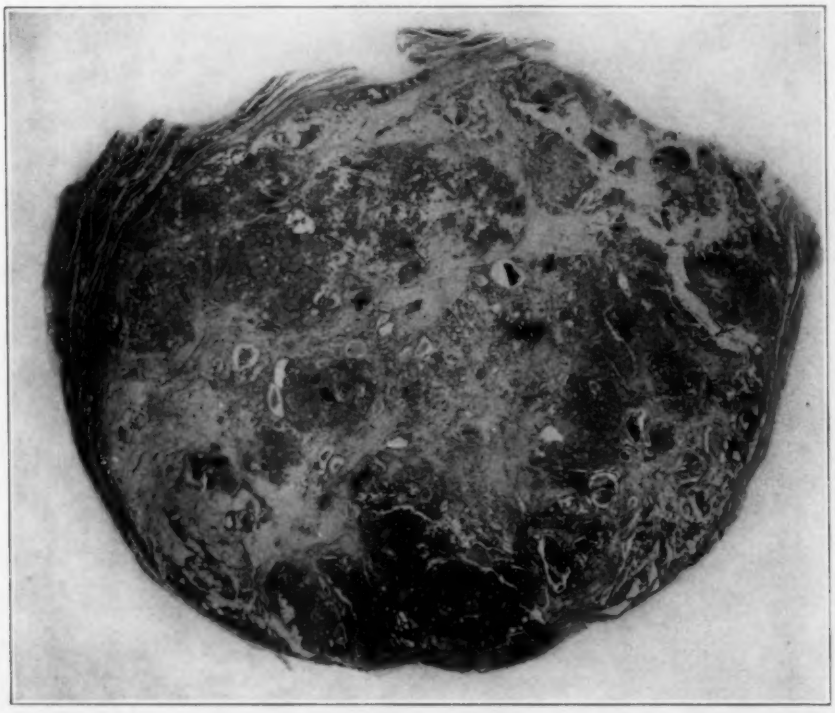

Fig. 17.—Low power magnification of a fetal nodule, showing marked secondary changes of hemorrhage cyst formation and scarring.

being aggregated near the periphery close to the parent epithelium and widely scattered toward the center (fig. 1). As the colloid which originally supported the acini and blood vessels disappears, the capillaries dilate and rupture with resultant hemorrhage. Once hemorrhage has occurred, the initial picture is altered, and secondary changes, such as necrosis, cyst formation, scarring, hyalinization and calcification, may ensue, serving to alter or completely destroy the appearance of the initial nodule.

In the material examined, we were unable to trace any relationship between growth and carcinoma. However, in going over our material, Dr. Douglas Symmers suggested that the mode of origin herein demonstrated tends to support the belief that this type of lesion is sometimes prone to develop carcinoma because, although the new hyperplastic acini may become normally functioning thyroid epithelium, the abnormal method of their development may become still further diverted.

CONCLUSIONS

1. The nodule known as "fetal adenoma" is composed of regenerating thyroid epithelium, occurring in a colloid follicle or body.

2. This follicle may be small or large and encapsulated or non-encapsulated.

3. The peculiar appearance is due to the fact that the proliferation of epithelium occurs into the colloid, which supports the growth, eliminating the immediate necessity of fibrous supporting tissue.

4. In the larger nodules, as the colloid disappears the acini are left without apparent supporting tissue, except for the capillaries, which may become markedly dilated, thus giving rise to the peculiar appearance of the central portion of these growths.

5. Once the lesion is fully formed, there are four possibilities:

(*a*) The acini may function as normal thyroid epithelium.

(*b*) They may undergo hyperplasia, forming the nodular hyperplastic goiter, or so-called toxic adenoma.

(*c*) They may become carcinomatous.

(*d*) Hemorrhage may occur into the nodule followed by secondary degenerative changes, such as necrosis, cyst formation and fibrosis.

EXPERIMENTAL JOINT SPRAIN

PATHOLOGIC STUDY

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AND

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In a previous communication [1] the pathologic changes which followed the production of mild sprain in the knee joint of the rabbit were reported. Since that time, other similar experiments have been performed which are of greater interest, particularly since the results suggest the pathologic basis for the clinical condition termed chronic traumatic arthritis. As a foundation for the discussion, a résumé of the results in the most recent group of experiments together with those reported [2] previously is given.

METHOD

After varying amounts of manual force were applied to the knee and ankle joints of ten rabbits, a method was developed for the production of mild and severe forms of sprain without roentgenographic evidence of fracture.

In this manner, mild sprains were produced in twelve rabbits (group 1) and severe sprains in eleven (group 2). Roentgenograms of all sprained joints were taken immediately thereafter, and no evidence of injury to the bone was demonstrated. Autopsy was performed on the animals in group 1 in from one to six weeks after production of the sprain and on those in group 2 in from one to eleven weeks later. The joints were removed, roentgenograms were again taken and the specimens were examined grossly and microscopically.

Mild and severe sprains were produced in the same manner in a third group of twelve rabbits, and the sprained knee joints were immobilized in plaster of paris casts. Attempts were made to determine the effects of immobilization on the rate of healing, but since it was difficult to maintain satisfactory immobilization, the results were discarded.

RESULTS

Pathologic Changes After Mild Sprain (Group 1).—One week after mild sprain there was definite swelling of the joints. The synovial

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1. Miltner, Leo J., and Hu, C. H.: Experimental Reproduction of Joint Sprain, Proc. Soc. Exper. Biol. & Med. **30**:883, 1933.

2. Miltner, Leo J.; Hu, C. H., and Fang, H. C.: The Pathology and Treatment of Joint Sprain, Chinese M. J. **49**:521, 1935. Miltner and Hu.[1]

membrane was edematous and had small foci of hemorrhage (fig. 1) and a few dilated blood vessels near its surface. The joint fluid was increased in amount and was more viscous and yellower than normal. There was slight pannus formation at the osteocartilaginous junctions on the injured side. The subcutaneous tissue and the loose connective tissue of the mesotendons showed evidence of hemorrhage. There was no blood within any of the tendon sheaths. Microscopic sections showed hemorrhage into and under the synovial membrane. The synovial cells showed marked vacuolation. The subsynovial tissue was edematous, with capillary congestion, early fibroblastic proliferation and considerable infiltration with leukocytes and lymphoid cells. In places the surface of the synovial membrane was covered with fibrin, while in

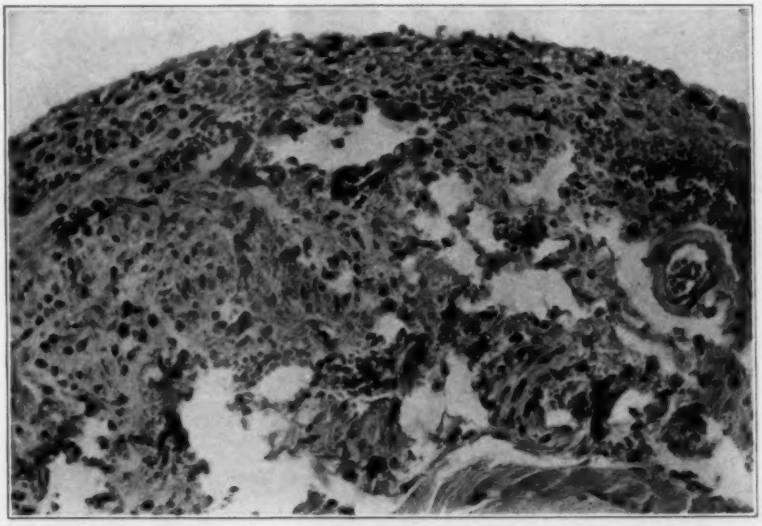

Fig. 1.—Photomicrograph (× 200) of the synovial membrane of a joint one week after mild sprain. Note the edema and foci of hemorrhage and early proliferation of fibroblasts in the loose subsynovial connective tissue. Other sections in the same area show infiltration with leukocytes and lymphoid cells.

others the fibrin was seen in the subsynovial tissues. Near the attachments to the bone, the injured capsule and ligaments showed similar changes consisting of edema, fibroblastic proliferation and infiltration with lymphoid cells. The loose connective tissue beneath the synovial lining of the tendon sheaths presented a picture essentially the same as that seen in the synovia.

Two and three weeks after the sprain there were still definite signs of acute inflammation of the synovial tissue. There was a great increase in the number of fibroblasts in the subsynovial tissue. Hemosiderin was found in large amounts in the phagocytic cells of the inflamed area.

At this stage hyalinized masses of fibrin were seen within the synovial tissue and on the synovial surface (fig. 2). The tendon sheaths and the soft tissue surrounding the capsule and ligaments showed changes similar to those which were found after one week, except that there was more marked fibroblastic proliferation.

After four weeks, there was no external evidence of swelling or other signs of old injury. Microscopic examination of the tendon sheaths, synovial tissue and ligaments still showed evidence of old hemorrhage. The number of fibroblasts was decreased, but the number of collagen fibers was increased. Many small capillaries were seen in this young connective tissue. In certain places the synovial membrane showed small foci of necrosis, with deposits of fibrin on the surface. There

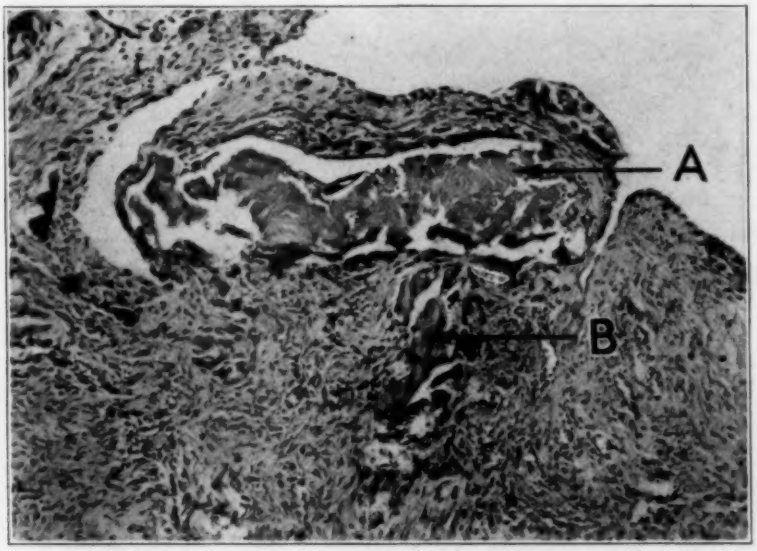

Fig. 2.—Photomicrograph (× 180) of the synovial membrane of a joint three weeks after mild sprain. Note the hyalinized mass of fibrin (*A*) between the villi and (*B*) within the subsynovial connective tissue.

was still an appreciable amount of edema of the loose connective tissue, but the infiltration with leukocytes and lymphoid cells was much less than that shown in the sections taken after three weeks.

Microscopic examination at six weeks showed complete healing of the traumatized parts. There was a late stage of fibrosis, with shrinkage and contraction of the connective tissue structures.

Pathologic Changes After Severe Sprain (Group 2).—In addition to the changes just described (after mild sprain), the joints subjected to severe sprain showed the following pathologic changes: A fibrillar degeneration of the surface layers of the cartilage was seen, especially

at the margins of the joint surfaces on the affected side. New fibroblasts, apparently arising from the synovial membrane, had already attached themselves over these areas of cartilage as early as the second week. The inner free portion of the semilunar (fibrous) cartilage on the affected side showed slight necrotic changes. After six weeks, the distal free ends of the semilunar cartilage showed a more advanced stage

Fig. 3.—Photomicrograph (× 234) of the hyaline cartilage on the side of the joint (side of compression) opposite to the sprained ligaments, ten weeks after severe sprain. Note that many of the cartilage cells of the intermediate area (*I*) show only faint staining, while others have degenerated completely.

of the fibrillation with exfoliation of the superficial layers and hyalinization of the deeper layers of cells. At the end of the eighth and tenth weeks, several specimens showed complete degeneration of the free portion of the semilunar cartilage. In all the specimens the intra-articular cartilage of the tibia on the side of the joint opposite to the

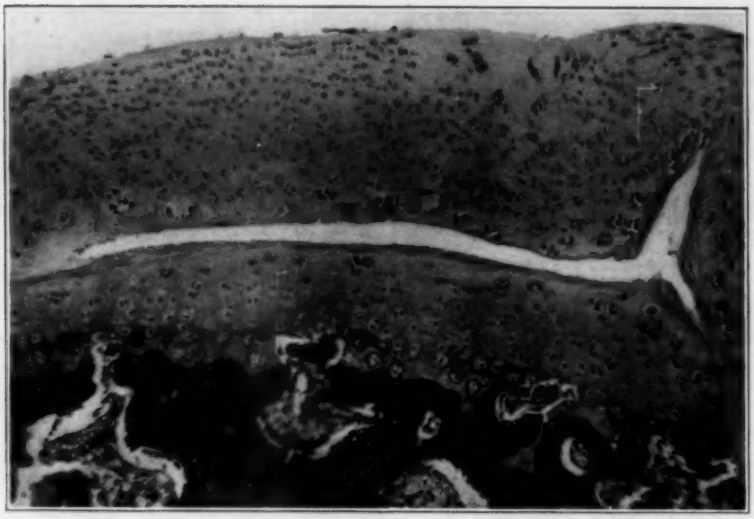

Fig. 4.—Photomicrograph (× 70) of the hyaline cartilage ten weeks after severe sprain. Note the horizontal fissure caused by trauma. Numerous necrotic cartilage cells may be seen at the margins of the fissure.

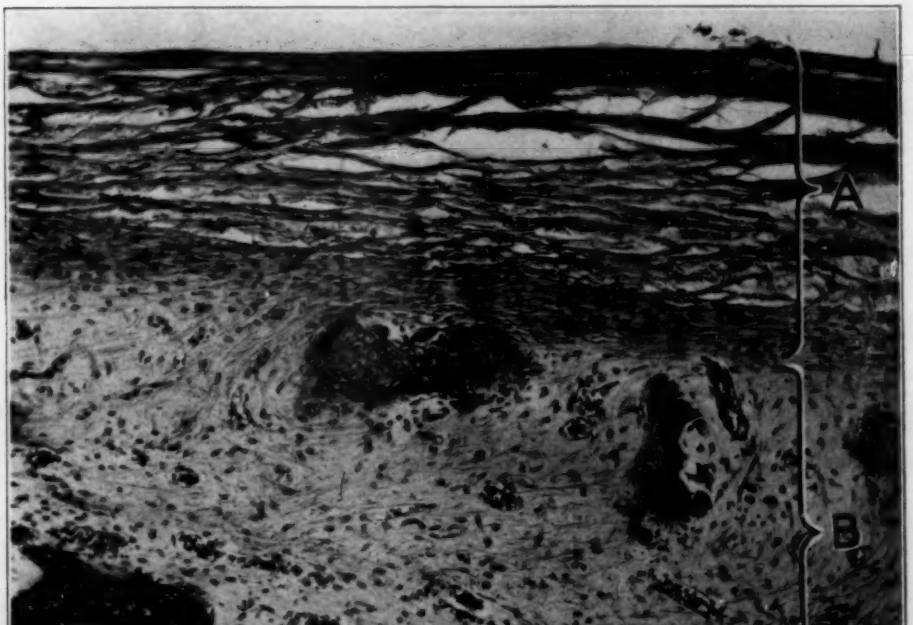

Fig. 5.—Photomicrograph (× 113) of the point of insertion of ligament into bone eight weeks after severe sprain. Note (*A*) the ligament and (*B*) the typical area of vascular callus with detached bits of bone which failed to cast a shadow in roentgenograms.

sprained ligaments showed numerous scattered cartilage cells, which were faintly or heavily eosinophilic in contrast to the normal cartilage cells which had taken up a deep basic stain. These eosinophilic cartilage cells showed other definite evidence of degeneration, such as fragmentation of the nuclei and shrinking of the cytoplasm (fig. 3). A horizontal fissure within the substance of the articular cartilage was found in one knee joint (fig. 4). In most of these specimens microscopic examination showed definite evidence of a tearing injury at the point of insertion of ligaments into the bone. Small bits of bone had been torn loose and tended to grow in the new location (fig. 5). At these points of insertion of ligaments there was a large increase of the fibroblasts with vascular dilatation and infiltration with round cells. Here, the process of repair persisted for as long as from eight to ten weeks. The synovial membrane showed a persistence of the previously described inflammatory changes for as long as from six to eight weeks.

COMMENT

These experiments demonstrate that trauma applied to joints causes an acute inflammatory reaction at the points of greatest injury. If the injury is severe enough, the bony or cartilaginous structures may be involved. These structures heal slowly under ordinary circumstances; therefore, the inflammation may become chronic. In the mild form of sprain there is an immediate response of the most vascular structures. The early increase in the activity of the synovial membrane with the exudation of synovial fluid is a condition which is known clinically as traumatic synovitis. At the same time there is edema of the loose subsynovial tissues and of the loose periarticular connective tissues, especially those near the tendon sheaths on the affected side of the joint. In the joints of the rabbits in group 1 (those with mild sprain) the external signs and gross evidence of pathologic change disappeared by the fourth week, but the microscopic evidence of inflammation (slight edema and fibrosis of the connective tissues) persisted until the end of the sixth week. This change is of clinical interest, since it suggests that the joint should be protected or supported for at least two weeks after the clinical signs have disappeared.

In the joints of the rabbits in group 2 (those with severe sprain without roentgenographic evidence of fracture) the inflammatory reaction of the soft tissues was similar in nature but more severe in degree than that found in the joints of the rabbits in group 1. The microscopic changes of the soft tissues usually persisted until the sixth to the eighth week and resolved gradually during the eighth to the tenth week. In addition to the microscopic changes found in the joints of the rabbits in group 1, there were evidences of injury at the point of insertion of

ligaments into the bone and of the joint cartilage. At the ligamentous-osseous junctions detached bits of bone were usually seen. These bits of bone were microscopic in size and failed to throw a shadow in the roentgenograms.

Of greater interest were the changes in the intra-articular hyaline cartilage of the tibia on the side of the joint opposite to the sprained ligaments. Since the normal cartilage covering the surface of the tibia is approximately twice as thick as that which covers the convex surface of the corresponding condyle of the femur, it is believed that its intermediate or less compact area is more subject to a compression type of injury. The uniform finding of degeneration of the cells in the intermediate zone of the cartilage bears out this contention. It is further believed that this slow degeneration of the cartilage may produce not only local but remote effects on the more vascular structures of the joint and that therein lies one of the causes for the condition termed chronic traumatic arthritis. The traumatic fissure in this intermediate zone of the cartilage, although found in only one case, also adds evidence to show that this tissue is vulnerable to ordinary trauma.

SUBPHRENIC ABSCESS

AN ORIGINAL EXTRAPLEURAL OPERATION

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A subphrenic abscess may be defined as one which at some point is in contact with the under-surface of the diaphragm. Barlow described the condition in 1845, while Volkmann recorded the first operation in 1879.

It is my purpose to emphasize the importance of early diagnosis and operation, to report my cases and also an original, safer, transcostal, extrapleural method of drainage and to point out the necessity for choosing the most suitable operative route, depending on the location and the size of the abscess.

The subphrenic area is considered to be that space bounded above by the diaphragm and below by the transverse mesocolon. This space may be divided for clinical purposes into a suprahepatic and an infrahepatic space, and these may be divided into lesser but less completely separated spaces. A subphrenic abscess may occupy all or only a part of one or more adjoining spaces, depending on limiting adhesions.

The subphrenic space is divided as follows:

1. The suprahepatic space
   - Right intraperitoneal anterior superior space
   - Right intraperitoneal posterior superior space
   - Right extraperitoneal superior space, between the layers of the coronary ligament
   - Left intraperitoneal anterior superior space
2. The infrahepatic space
   - Right intraperitoneal inferior space
   - Left intraperitoneal inferior anterior space
   - Left intraperitoneal inferior posterior space (bursa omentalis)
   - Left extraperitoneal inferior retrosplenic space (Barnard[1])

A subphrenic abscess originates from a perforated peptic ulcer in about one third of the cases and from a suppurative appendicitis in

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Read before the Western Surgical Association, Dec. 12, 1936.

1. Barnard, H. L.: Surgical Aspects of Subphrenic Abscess, Brit. M. J. 1:371, 1908.

a third. It occurs frequently by direct extension from the appendix along the outer gutter of the ascending colon into Morison's pouch. Occasionally it may follow an infection or an injury to the liver, gallbladder, pancreas, colon, spleen or kidney or to other abdominal structures (Harper and Thomas [2]).

Rarely it may result from a metastatic infection, from extension of an infection from above the diaphragm or from osteomyelitis of a vertebra (Barnard).

The importance of the lymphatics in carrying infection from the colon and especially from the ileocecal region has been emphasized by Truesdale.[3]

Some abscesses which occur in the right posterior extraperitoneal space after a subsiding appendicitis, as in case 6, undoubtedly arise from infection along the lymphatics.

Subphrenic abscess occurs about three times more frequently in males than in females (Ochsner and Graves [4]). This may be due to the greater frequency of perforated peptic ulcer and of appendicitis in the male. Ochsner and Graves found that 70 per cent of the abscesses they observed occurred in persons from 9 to 40 years of age. They observed that only about 30 per cent of subphrenic infections went on to suppuration, the remainder subsiding spontaneously.

Anatomically, the superior surface of the liver, like the right surface and the most of the anterior surface, lies directly against the diaphragm and is curved corresponding to the dome of that structure. The superior surface reaches higher up on the right than on the left, while the center is slightly depressed. The junction of the superior and the posterior surfaces forms a rather blunt margin. The uneven posterior surface is shaped somewhat like a rectangular triangle. It is curved so as to be convex on the right side. From right to left may be found the fossa venae cavae, the impression for the adrenal gland, the lobus caudatus, the fossa ductus venosi and the impression for the abdominal esophagus. The liver is covered for the most part by the tunica serosa. There are four or five small areas and one fairly large one on the posterior surface of the right lobe which lie extraperitoneally.

Anteriorly, the ligamentum falciforme hepatis passes from the abdominal wall and the diaphragm near the midline to the superior

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2. Harper, F. R., and Thomas, C. A.: Subphrenic Abscess Following Trauma, J. A. M. A. **105**:1267 (Oct. 19) 1935.

3. Truesdale, P. E.: Origin and Course of Infection in Subphrenic Abscess, Ann. Surg. **98**:846 (Nov.) 1933.

4. Ochsner, A., and Graves, A. M.: Subphrenic Abscess: Analysis of 3,372 Collected and Personal Cases, Ann. Surg. **98**:961 (Dec.) 1933.

surface of the liver. At the cardiac impression of the liver the two layers forming the peritoneal fold diverge from one another and go over into the anterior lateral layers of the ligamentum coronarium hepatis from the inferior surface of the diaphragm approximately in a frontal plane to the upper surface of the liver. The peritoneum forming the posterior layers of the coronary ligament comes from the posterior surface of the diaphragm or from the anterior surface of the right kidney, the adrenal gland or the flexura coli dextra and is sometimes called the ligamentum hepatorenale (Spalteholz [5] and Cunningham [6]).

On the left the anterior and posterior layers of this ligament come together quickly and form the ligamentum triangulare sinistrum hepatis. At the right of the fossa venae cavae the anterior and posterior layers of peritoneum are widely separated, leaving a large uncovered area on the posterior surface of the liver, which is limited at the right by their junction into the ligamentum triangulare dextrum hepatis.

There is considerable normal variation in the level of reflection of the pleura at the costophrenic angles, forming a variable width of extrapleural diaphragm through which transcostal drainage of a subphrenic abscess might be established. Corning [7] pointed out that the height of the diaphragm varies at different ages. In the new-born infant it may be found at the level of the fourth rib on the right side. In a 36 year old man the diaphragm may be midway between the fifth and the sixth rib, while in a 72 year old man it may be below the sixth rib (fig. 1). In the presence of emphysema one will find the diaphragm lower than usual, and when there are old pleural adhesions it may be somewhat fixed, increasing the difficulties of diagnosis.

SYMPTOMS AND DIAGNOSIS

The symptoms of a subphrenic abscess vary to a large extent, depending on the source, location and size of the abscess. Elsberg [8] pointed out that they may develop days, weeks or months after an attack of appendicitis or an operation. Usually there is a history of a recent acute attack of appendicitis, cholecystitis, a perforated peptic ulcer or an operation. The temperature may persist or drop temporarily and then

5. Spalteholz, W.: Atlas of Human Anatomy, ed. 3, translated by L. F. Barker, Philadelphia, J. B. Lippincott Company, 1910.

6. Cunningham, J. D.: Text-Book of Anatomy, ed. 6, New York, William Wood & Company, 1931.

7. Corning, H. K.: Lehrbuch der topographischen Anatomie für Studierende und Aerzte, ed. 3, Wiesbaden, J. F. Bergmann, 1911, p. 283.

8. Elsberg, C. A.: A Contribution to the Pathology, Diagnosis, and Treatment of Subphrenic Abscesses After Appendicitis, Ann. Surg. **34**:729, 1901.

increase steplike each day, with an increase of systemic toxemia together with local symptoms of suppuration.

The peritoneum over the diaphragm is supplied from the phrenic nerve; consequently inflammation may cause referred pain in the shoulder and neck, where it is supplied by cutaneous nerves from the fourth

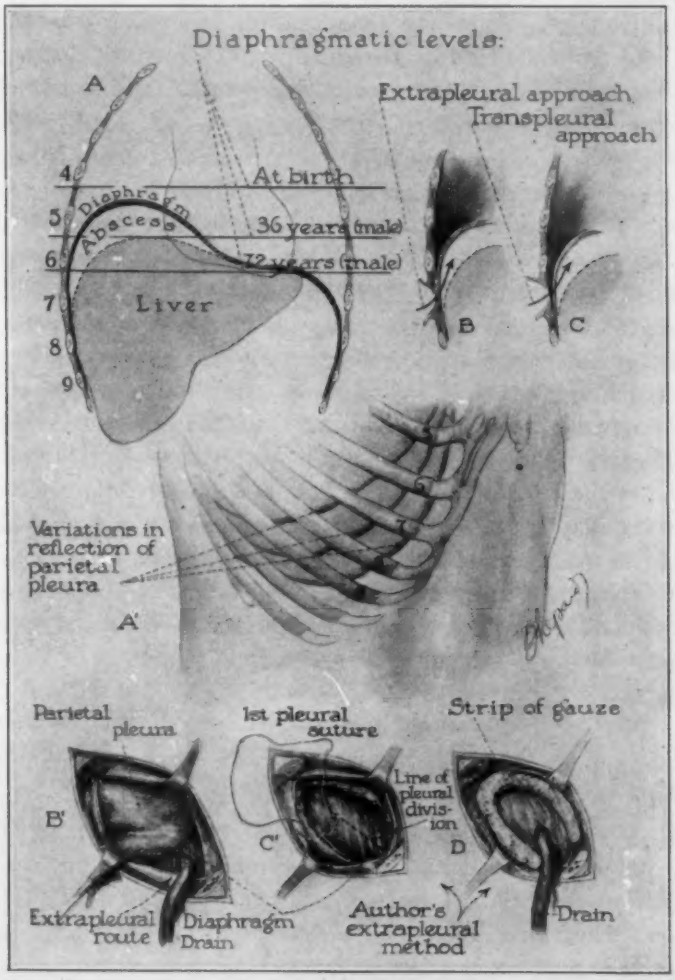

Fig. 1.—*A* and *A'* show normal variations in the height of the diaphragm and its pleural reflections. In *B* and *B'* is shown the transcostal extrapleural method of drainage, which may be used with a high pleural reflection; in *C*, the transcostal route which is frequently used to open the pleural cavity in the absence of adhesions; in *C'* and *D*, my method. In the last method, after resection of one rib in the axillary line, the costal and diaphragmatic pleural layers are incised, and the edges are dissected laterally and sutured, forming an extrapleural area on the diaphragm for drainage.

cervical segment (Christopher [9]). The lateral and anterior portions of the abdominal peritoneum are supplied by the lower intercostal and first lumbar nerves, and the central posterior and the pelvic portions of the peritoneum, chiefly by the sympathetic system (Cope [10]).

At the onset there may be limited or painful respirations owing to immobilization of the diaphragm or to a pleuritis, which is more marked in the case of a suprahepatic abscess and less noticeable when the abscess is located below the reflection of the pleura. Later there is practically always limitation of movement of the diaphragm, but the amount of elevation is variable, depending on the size and location of the abscess.

A fluoroscopic examination or roentgenograms taken from several angles and with the patient upright may fail to demonstrate a small

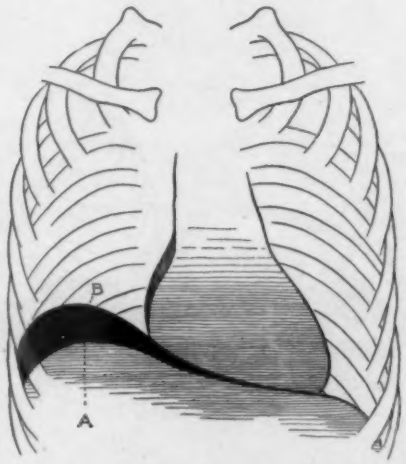

Fig. 2 (case 3).—Drawing made from roentgenograms which at the onset of symptoms showed only slight elevation of the diaphragm (*A*), but one week later (*B*) there were marked elevation of the diaphragm and also distortion of the heart due to an abscess of the superior anterior space which contained no gas.

suprahepatic abscess. When the abscess is large there may be extension forward and downward, with a visible swelling and an area of dulness over the abdomen forming a triangle bounded by the falciform ligament, the transverse colon and the right costal border.

In cases in which the diagnosis is doubtful examinations should be repeated in a few days, and a comparison made of the level and immobility of the diaphragm (fig. 2 *A-B*). In a few cases gas and a shifting

9. Christopher, Frederick: Neck Pain in Subphrenic Abscess, Ann. Surg. **85**:318, 1927.

10. Cope, V. Zachary, in Walton, A. J.: A Text-Book of Surgical Diagnosis, New York, William Wood & Company, 1928, chap. 2, p. 697.

fluid level can be demonstrated both by roentgenographic and by physical examination (fig. 3).

The early friction sounds and symptoms of pleuritis over the costophrenic region may disappear with effusion in the pleural cavity. It is often difficult to establish a differential diagnosis between abscess and bronchitis, pulmonary inflammation, pleuritis or atelectasis. The diagnosis was correct in only 38 per cent of the 18 cases reported by Brown.[11] Fever and the degree of toxemia, as indicated by a marked leukocytosis, vary with the acuteness and activity of the abscess but are increased out of proportion to the pulmonary findings.

An abscess involving the suprahepatic posterior intraperitoneal space may differ roentgenographically from one involving the anterior space in that in the anteroposterior view of the former the costophrenic

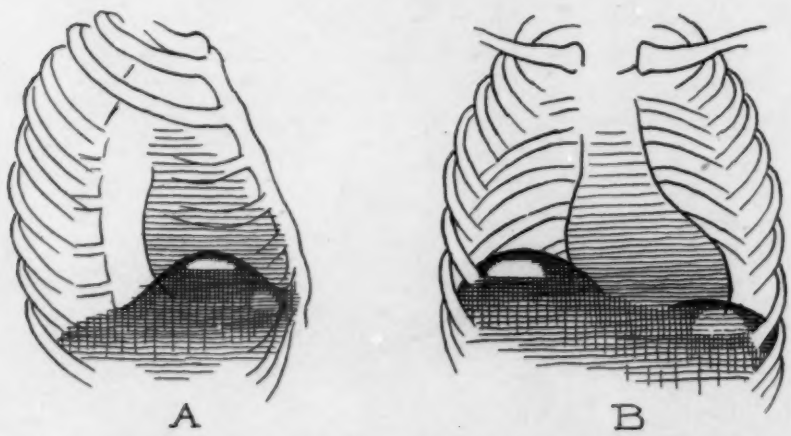

Fig. 3 (case 4).—Elevation of the diaphragm due to an abscess containing gas. There was slight increased density in the lower lobe of the lung. Transcostal extrapleural drainage was done (fig. 1, *C'* and *D*).

instead of the cardiophrenic angle is obliterated and in the lateral view the posterior instead of the anterior costophrenic angle is obliterated.

When the abscess involves the right posterior extraperitoneal space the roentgenograms may show little elevation of the diaphragm, although in the lateral view the posterior costophrenic sinus may be obliterated.

In the case of a large subphrenic abscess the roentgenograms may show a patchy area of increased dulness in the lower lobe of the lung, which may be definitely above the lower edge, the result of atelectasis or peribronchial inflammation following immobilization and elevation of the diaphragm. There are frequently increased hilus markings in both lungs, especially in the right.

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11. Brown, H. P., Jr.: Subphrenic Abscess, Ann. Surg. **93**:1075, 1931.

In the case of a subhepatic abscess on the right side the liver may push the diaphragm up with limitation of motion, but there is no gas beneath it.

If the abscess is large there may be an abdominal swelling beneath the liver or in the loin in addition to local tenderness, muscle spasm and rigidity.

Dulness from a subhepatic abscess may extend below the liver, outlining the triangle formed by the falciform ligament, the transverse colon and the costal border, similar to that caused by an abscess of the anterior suprahepatic space. Tenderness and bulging in the right loin occur frequently with a subhepatic abscess as well as with an abscess in the posterior superior space.

Diagnosis is often delayed, even when there are positive roentgenographic signs, owing to the lack of clinical recognition of the condition. When there is gas beneath the diaphragm, physical examination with the patient in the recumbent position may show diminution or absence of hepatic dulness anteriorly and a high axillary dulness which shifts when the patient turns or sits up.

A persisting local tenderness is quite suggestive. A widening of the right side of the chest due to elevation of the lower ribs was observed in case 5, that of an extraperitoneal abscess, without elevation of the diaphragm.

The first symptoms may be either thoracic or abdominal and vary from pleuritis, jaundice, a local swelling and pain or tenderness to those of a spontaneous perforation.

There is often an incubation or quiescent period of a week or ten days, the only symptoms being slight fever and an increased leukocytosis.

After an abscess has formed a defense zone of adhesions, the earlier it is drained the less will be the chances of a fatal issue as a rule. One might suggest delay to permit development of further overlying pleural or peritoneal adhesions, except that rupture, sepsis and pyemia may suddenly develop. Usually after a brief period the abscess increases rapidly in size, and the toxic symptoms become marked. There may be extension of infection through the diaphragm into the pleural cavity, retroperitoneally by way of the lymphatics into the mediastinum or into the peritoneal cavity.

The less frequent intrahepatic abscess is more likely to produce chills and pain referred to the region of the right scapula (Elsberg). A foul odor is more likely to be associated with a subphrenic than with a hepatic abscess. A perinephritic abscess should give rise to some evidence of renal infection, and the intravenous urogram will aid in the diagnosis.

One should consider the possibility of a postoperative subphrenic accumulation of bile due to leakage or injury of the bile ducts, as in the following case.

Recently I removed 3,000 cc. of sterile bile from the right superior anterior subphrenic space, which extended down to the transverse colon. The patient, a 32 year old man, had been operated on three weeks before by another physician, who removed the gallbladder and gallstones. The drain was removed on the second day, and the wound healed. At the operation a segment of the hepatic duct had been excised, and sterile bile had collected beneath the diaphragm with limiting adhesions of the colon. There was little jaundice for the first ten days and slight elevation of the diaphragm. The patient was very weak after the operation and became progressively worse, with little fever and acholic stools. Shortly before drainage, the jaundice became intense, and there was marked elevation of the diaphragm.

After the wound was reopened and the bile drained, I found that the cut ends of the hepatic and common ducts were too indurated and widely separated to suture. A gap of 1 inch (2.5 cm.) was bridged with a rubber tube which extended into the duodenum. Drainage of bile stopped after six weeks.

The patient has gained 30 pounds (13.6 Kg.) and is well after three months.

PROGNOSIS

The prognosis of a subphrenic abscess is always grave, and it is important to operate before the development of sepsis or intrathoracic complications.

The mortality from subphrenic abscesses is somewhat variable but always high (Giertz[12]). Lockwood[13] reported it to be 33.3 per cent in the cases in which operation was performed and 96.8 per cent in those in which it was not performed. Ochsner and Graves found it to be 32 per cent in their cases of abscess, in which the sources varied, while Bevan[14] stated that it was about 50 per cent in cases of abscess which occurred following appendicitis. Some complications are unavoidable, owing to extensive peritonitis or to a severe original infection.

Aspiration of a subphrenic abscess should be avoided before and if possible at operation, since it is likely to result in empyema or peritonitis, unless adhesions which are difficult to demonstrate are present.

Lockwood found that 41.9 per cent of deaths were due to intrathoracic complications.

Ochsner and Graves found that of 189 patients who were operated on without the pleura or the peritoneum being opened, 21 per cent died; of 305 on whom transpleural drainage was done, 39 per cent died, and of 307 on whom transperitoneal drainage was done, 35.5 per cent died. In 7 cases of their own in which the pleural cavity was opened at operation, the mortality was 85 per cent.

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12. Giertz, K. H.: Twenty-Five Years' Experience in the Treatment of Peritonitis, Ann. Surg. **104**:712, 1936.

13. Lockwood, A.: Subdiaphragmatic Abscess, Surg., Gynec. & Obst. **33**:502, 1921.

14. Bevan, A. D.: Present Status of the Problem of Appendicitis, S. Clin. North America **16**:63, 1936.

Barnard reported the development of empyema in 56 of 76 reviewed cases.

A patient with chronic empyema which developed after a drainage operation for subphrenic abscess came under my care recently.

Three months previously this 26 year old man was operated on, and a ruptured appendix was removed four days after the onset of symptoms, with drainage. Ten days later pain developed in the right upper abdominal quadrant, and after five days' observation, including roentgen examination, a subphrenic abscess was drained. The ninth and tenth ribs were resected posteriorly, followed by drainage and healing of the wound. Immediately after the operation the patient suffered from severe pain in the right side of the chest with dyspnea. The pain gradually became worse, and one month later 4 quarts (3.7 liters) of pus was drained from an empyema on the right side. The drainage tube was removed too soon, and the patient came into the hospital quite toxic.

Immediately after the insertion of a catheter into the old sinus and drainage of a large empyema cavity, he obtained relief, but further surgical treatment will be necessary.

There is a need for a safer one stage transcostal drainage operation in which the pleural cavity need not be contaminated. The anterior and posterior subcostal incisions are too far from the small suprahepatic abscesses, which makes it difficult to avoid opening and contaminating the peritoneal cavity.

AUTHOR'S CASES

In my 9 cases all the patients were males. Two deaths occurred, making a mortality of 22.23 per cent. In all the cases the abscess was on the right side, and a drainage operation was performed in each. The ages of the patients varied from 14 to 59, the average being 34. The ages of the 4 patients having perforated ulcers varied from 32 to 59, the average being 42, while the ages of the 4 with appendicitis varied from 14 to 52, the average being 25.

There were 2 cases of perforated duodenal ulcer and 2 of perforated gastric ulcer, in 3 of which operation was performed.

There were 4 cases of acute appendicitis, in only 1 of which had operation been performed, and then for a pelvic abscess.

The length of time from rupture of the viscus or the onset of acute appendicitis to the onset of symptoms of the subphrenic abscess varied from one to sixteen days and it averaged eight days. The symptoms were then present from eight to thirty-nine days and averaged nineteen days before drainage. This was an average of twenty-seven days from the onset of the original infection to operation.

The temperature during most of the course of the abscess was rarely over 102 F., but before operation there was usually a steplike rise, with increased toxemia and a slight drop in the white cell count. The number of white cells varied from 7,000, a count made after per-

Data on the Author's Nine Cases of Subphrenic Abscess

Case	Sex	Age, Years	Source of Abscess and Days Before Drainage	Previous Operation	Time Between Onset of Source to Onset of Symptoms, Days	White Blood Cell Count	Location of Abscess in Subphrenic Space; Contents of Abscess	Method of Drainage	Complications and Result
1	M	59	Perforated duodenal ulcer; 39	0	0	21,900	Right superior anterior space; 2,000 cc. + gas	Transcostal route, 10th rib; extrapleural method	Cured; sinus 5 mo.
2	M	46	Perforated gastric ulcer; 22	+	11	30,900	Right superior anterior space; 2,000 cc.	Transcostal route, 10th rib; extrapleural method	Died; moribund at operation; bilateral bronchopneumonia
3	M	32	Perforated gastric ulcer; 46	+	18	10,240	Right superior anterior space; 300 cc.	Transcostal route, 9th rib; extrapleural method	Cured 1 yr. and 9 mo.; sinus 2 mo.
4	M	32	Perforated duodenal ulcer; 15	+	6	28,150	Right superior anterior space; 500 cc. + gas	Transcostal route, 8th rib; author's extrapleural method	Cured 1 yr.; sinus about cartilage; resected 4 mo. later
5	M	17	Acute appendicitis; 35	0	7	20,950	Right extraperitoneal superior space; 500 cc. Staph. albus on culture	Posterior transcostal route, 12th rib	Cured; sinus 2 mo.
6	M	14	Appendicitis with perforation; 17	0	9	16,300	Right superior posterior space; 1,000 cc.	1. Transcostal route, 10th rib; exploration of peritoneal cavity extrapleurally 2. Posterior subcostal route, 12th rib	Cured; pelvic abscess drained by rectum before symptoms of subphrenic abscess developed
7	M	18	Appendicitis with perforation; 15	0	6	20,900	Right superior posterior space; 800 cc.	Posterior subcostal route, 12th rib	Died 10 days postoperatively; bronchopneumonia of left lung and empyema
8	M	52	Appendicitis with perforation; 23	0	9	14,400	Right superior posterior and right inferior spaces; 3,000 cc.	Posterior subcostal route, 12th rib	Cured; sinus 2 mo.
9	M	42	Perforated gallbladder; 35	0	10	7,000	Right inferior and part of right superior anterior spaces; 75 cc.; colon bacilli on culture	Anterior subcostal route; right rectus incision; cholecystectomy and drainage	Cured 3 yr.; sinus 3 wk.

foration of a gallbladder, to 30,900, a count made twenty-two days after an operation for a perforated gastric ulcer, which was associated with bilateral pneumonia and terminated fatally. The average count made just before drainage was 18,900. With one exception, there was a higher white cell count in the cases in which the abscess was large. In this case the white cell count was 14,400 and there was 3,000 cc. of pus in the abscess cavity twenty-three days after the onset of appendicitis which was not treated surgically.

The symptoms suggesting a subphrenic abscess were first noted in the side of the chest in 4 cases, in 3 after a perforated ulcer and in 1 after appendicitis, while in 5 cases the first symptoms were abdominal, in 1 after an ulcer, in 3 after appendicitis and in 1 after perforation of the gallbladder.

The correct diagnosis was made before operation in 8 cases, or 88 per cent.

The subphrenic abscess was in the right anterior superior space in 4 cases, in all of which it followed a perforated ulcer. In 4 cases the abscess followed acute appendicitis; it was located in the right extrapleural superior space in 1 and involved the right posterior superior space in the other 3. In one of the latter it extended forward to the anterior abdominal wall into the inferior space and contained 3,000 cc. of pus.

In the case in which there were two separate perforations of the gallbladder there were two abscess cavities, one inferior to the liver and a smaller one just above the edge of the liver.

The size of the abscess varied from 75 to 3,000 cc., the average size being 1,040 cc. There was little difference in the size of the abscesses which developed following a perforated ulcer and of those which occurred after acute appendicitis.

There was gas in two abscess cavities, or 22 per cent, both of which occurred after perforated ulcers. The pus had a foul odor in 3 cases. Staphylococcus albus was cultured from the pus of an abscess which occurred after appendicitis, and colon bacillus was cultured from the pus of the one which occurred after a perforated gallbladder.

In 1 case in which abscess followed a perforated ulcer there was extensive bronchopneumonia on each side, and the patient was moribund at operation.

The other death was due to involvement of the opposite lung with pneumonia and empyema ten days after operation.

Most of the operative wounds drained from one to three months, but in 2 instances the period of drainage was longer and there were no recurrences.

The persistence of the high diaphragm laterally after a month of drainage, as shown by roentgenograms in cases 6 and 8, was probably

due to extensive adhesions, which explains the slow obliteration of these abscess cavities.

There have been no complaints as a result of the abscess and operation.

There was a recurrence of symptoms of ulcer in 1 case a year later, which necessitated medical treatment.

OPERATIVE TREATMENT

Drainage of a subphrenic abscess may be obtained through one of four regions, depending on the location and size of the abscess. The transcostal route may be chosen either anteriorly in the axillary line or posteriorly through the twelfth rib. The subcostal route may be used anteriorly through the abdomen or posteriorly beneath the twelfth rib and the level of the pleural reflection.

If the abscess is localized above the liver in the anterior superior space and beneath the dome of the diaphragm, extrapleural drainage should be established by resection of a rib in the axillary line directly above or as close to it as possible.

If an abscess is small, one may choose to resect the eighth rib, while for the larger abscesses, which extend lower, the ninth or tenth rib should be resected, since there is a wider extrapleural part of the diaphragm in this region and drainage should be established both as low and as posteriorly as feasible.

Elsberg has described the trancostal operation with resection of two ribs, the ninth and the tenth.

He established drainage through the diaphragm below the pleural reflection when it was possible, while in other cases he first obliterated the pleural cavity around the operative area by a circular suture between the pleural layers.

Occasionally the pleural cavity may be obliterated in this region by adhesions, or the pleural reflection may be elevated by pressure from the abscess (Boeckel [15]).

Lilienthal [16] and Parijsky [17] have been able to mobilize the costophrenic reflection of the pleura and push it upward, but Brown stated that this was not practical owing to frequent adhesions. It also necessitates the resection of two or more ribs, and the pleura may be torn and the pleural cavity contaminated.

While most surgeons attempt to obliterate the pleural cavity either by a circular suture or by a gauze pack, these procedures are not always satisfactory, even if the abscess is drained a few days later, as shown

15. Boeckel, cited by Ochsner and Graves.[4]

16. Lilienthal, H., in discussion on Ochsner and Graves,[4] p. 990.

17. Parijsky, cited by Ochsner and Graves.[4]

by frequent secondary empyema and high mortality (Elsberg and Ochsner and Graves).

Immediate drainage is usually advisable, since a few days' delay may result in sepsis and pulmonary complications.

In 4 of my cases the abscess was in the right anterior superior space and either localized beneath the dome of the diaphragm or extended well forward and laterally.

In cases 1, 2 and 3 I resected either the ninth or the tenth rib in the axillary line and opened the abscess through the diaphragm, below the pleural reflection, without opening the pleural or the peritoneal cavity (fig. 1 *B* and *B'* and fig. 2).

Since there is no test for determining the level of the costophrenic reflection, one cannot always avoid opening the pleural cavity in a transcostal operation unless adhesions are present or the pleural reflection is high.

In case 4 there was a relatively small localized abscess under the dome of the diaphragm (fig. 3). The eighth rib was resected in the anterior axillary line, and the pleural cavity, which extended quite low, was opened (fig. 1 *C*). A delay of several days before drainage of the abscess would have been necessary if the usual obliterative methods of suture or packing of the pleural cavity had been used, and there would have been the additional danger of empyema.

An original and simple method was devised to obliterate the pleural cavity and at the same time to make an extrapleural area of the diaphragm which could be safely incised, with immediate drainage of the abscess (fig. 1 *C'* and *D*).

The patient (case 4), a man aged 32, entered the hospital on June 13, 1935, complaining of severe pain in the upper part of the abdomen for three hours associated with vomiting. There were no previous symptoms, except that during the last two weeks he had noticed some gastric distress from one to two hours after meals, which was relieved by rest.

The past history was unimportant, except for an operation for removal of the appendix several years previously.

Physical examination revealed marked rigidity over the entire abdomen and a decreased area of hepatic dulness. The white cell count was 9,300.

An emergency operation was performed six hours after the onset of symptoms, and a perforated ulcer of the duodenum was sutured, with aspiration of free fluid.

Convalescence was good until the tenth day, when the patient had a temperature of 101 F. On the eleventh day there was some pain on the side of his chest and a leukocyte count of 28,150. On physical examination there were diminished breath sounds posteriorly and a lack of respiratory excursion of the diaphragm but no râles. With the patient in the recumbent position an area of high axillary dulness and one of tympany were noted over the region of the liver anteriorly. When he turned to either side the area of dulness and that of tympany shifted, suggesting a subphrenic abscess containing gas.

Fluoroscopic examination and roentgenograms showed an abscess cavity containing gas under the right side of a high fixed diaphragm (fig. 3).

Operation was performed on June 28, 1935, my original technic of transcostal extrapleural drainage being employed.

A local anesthesia was used, and about 2 inches (5 cm.) of the eighth rib was resected as low as possible in the anterior axillary line. The pleural reflection was so low that it was impossible to push it up without resecting another rib and perhaps accidentally opening the pleural cavity. A longitudinal incision was made through the costal pleura in the bed of the resected rib, starting about 1 cm. from the upper end (fig. 1 *C*). This pleural incision was continued downward to the pleural reflection and then upward through the diaphragmatic pleura to a point below the beginning of the anterior incision. The two edges of the diaphragmatic pleura with a thin layer of the underlying muscle were then dissected laterally. The lower edge of the pleura was widely approximated and sutured with two rows of fine catgut, without tension, to the overhanging free edge of the costal pleura and intercostal muscles, completely obliterating the pleural cavity. This suture line was completely covered with a narrow strip of gauze impregnated with petrolatum, which was sutured securely over it with fine catgut (fig. 1 *D*).

This procedure, with resection of only one rib, provided an extrapleural U-shaped diaphragmatic area about 3 cm. long and 1.5 cm. wide, which was entirely satisfactory for drainage of the underlying abscess. A small aspirating needle was inserted through this extrapleuralized portion of the diaphragm, and an abscess containing about 500 cc. of pus was located and opened by means of a small incision.

Convalescence was uneventful, with no symptoms of pleuritis, and the patient left the hospital one month later with a small amount of drainage. The cavity healed after about two months, but a sinus persisted at the lower end of the wound around the overlying cartilage. This was resected three months later, and the patient has had no further complaints.

On examination one year and nine months after operation the lungs showed no pleural thickening. The patient had regained his normal weight and had been working steadily for over one year.

For the suprahepatic abscess, one rubber tube is usually sufficient for drainage. For the large abscess associated with marked toxemia, a gradual decompression may be advisable.

The drainage tube should be sutured to the skin and daily irrigation employed. The size of the cavity should be determined from time to time by the injection of fluids or by roentgenographic visualization, and the tube should be shortened occasionally as obliteration occurs.

The abscesses of the subhepatic and posterior spaces may be drained more freely, but one should avoid extensive manipulation, and the forceful rib-spreading exploration of Lockwood in order to locate multiple cavities should be rarely necessary.

If a subphrenic abscess points in the upper part of the abdomen, extending forward either from the right superior anterior space or from the subhepatic space, it may be drained through an anterior abdominal incision.

The larger of these abscesses are limited medially by the falciform ligament, below by the transverse colon, which becomes adherent to the anterior wall, and laterally by the costal arch, which forms a bulging triangle of dulness in the upper portion of the abdomen.

The abdominal route was used in a majority of all cases reported by Gatewood.[18] However, there is danger of opening the general peritoneal cavity unless the abscess is walled off by adhesions well below the incision. Either a high rectus or an oblique subcostal incision may be used to drain an abscess pointing in this region.

The subcostal approach of Clairemont and Meyer [19] is intended to drain a high-lying suprahepatic abscess extraperitoneally. This incision extends parallel to the costal margin down to the peritoneum, which may be separated from the diaphragm by the finger without tearing it until the abscess is reached.

In case 9 of my series, after a perforation of the gallbladder from stones abscess cavities were localized beneath the liver and between it and the abdominal wall. The general peritoneal cavity was opened through a right rectus incision and both cavities opened and found to contain gallstones. The markedly diseased and perforated gallbladder, which contained other stones, was removed, with drainage anteriorly, and recovery resulted.

A large subhepatic abscess may point both posteriorly and anteriorly, but the posterior drainage route beneath the twelfth rib into Morison's pouch is usually easier and safer and provides better drainage than the anterior route.

If the abscess is localized in the upper part of the posterior superior space or above that in the extraperitoneal space, the twelfth rib may have to be dislocated upward, or resected as advocated by Ochsner and Graves, and the peritoneum separated from the under-surface of the diaphragm until the abscess is reached. In either instance, but especially in the latter, the costophrenic sinus may be found obliterated with the abscess directly against the lower ribs.

In cases 6, 9 and 8 the right posterior superior space was involved, with bulging in the loin. In case 6, in which the bulging extended well forward, the tenth rib was resected, the peritoneal cavity was explored through the extrapleural part of the diaphragm and the abscess was opened well back under the liver. A second small incision was made posteriorly beneath the twelfth rib directly into the abscess cavity, and drains were inserted. The peritoneal cavity around the transcostal extrapleural incision was walled off with an iodoform gauze pack, and the patient had an uneventful convalescence.

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18. Gatewood: Subphrenic Abscess, Am. J. M. Sc. **180**:398, 1930.

19. Clairemont, P., and Meyer, M.: Erfahrungen über die Behandlung der Appendicitis, Acta chir. Scandinav. **60**:55, 1926.

In case 7 the abscess bulged only in the loin, while in case 8 it pointed both in the loin and anteriorly, with a large triangle of dulness. In each case the abscess was drained posteriorly by an incision beneath the twelfth rib, but in spite of this in case 7, one of extensive primary peritonitis, a fatal suppuration developed in the opposite lung, associated with empyema.

Posterior drainage beneath the twelfth rib is accomplished by the following technic:

A transverse incision is made posteriorly at the level of the spinous process of the first lumbar vertebra, which will avoid the danger of

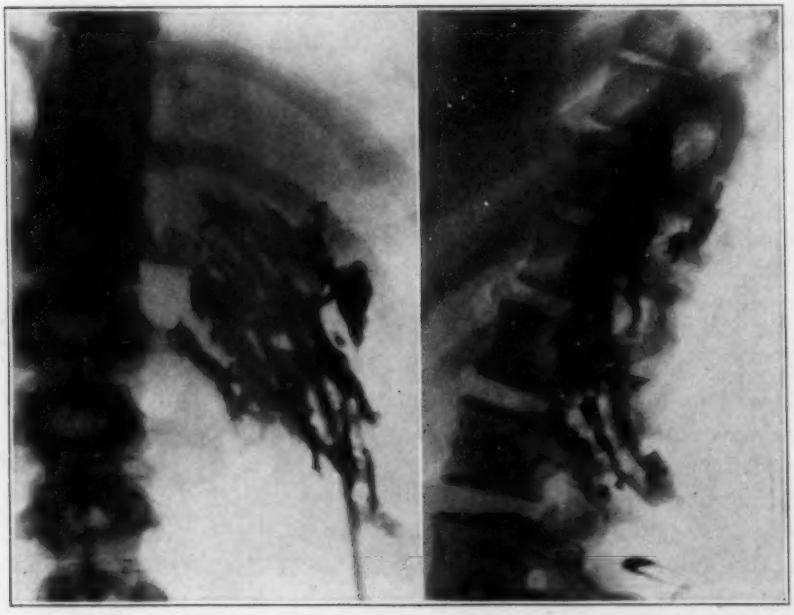

Fig. 4 (case 5).—Roentgenographic visualization of the right extraperitoneal abscess cavity ten days after resection of the twelfth rib and drainage. Elevation of the diaphragm was not present before operation.

opening the pleural cavity (Cunningham). The latissimus dorsi and the external oblique muscles and the deep fascia just lateral to the erector spinae muscles are split, and exploration for the abscess is made by blunt dissection beneath the peritoneum. Large abscesses extending downward and into the posterior superior pouch of Morison are easily palpated and opened into directly beneath the incision, and it is undesirable and rarely necessary to aspirate for diagnosis. Two large fenestrated rubber tubes, which are not too stiff or too long, are inserted for drainage and sutured to the skin with silkworm gut, and the wound with its separated muscle fibers is left open.

High-lying abscesses behind the liver may be opened by blunt separation of the peritoneum upward; occasionally a rib resection may be necessary, unless Bevan's method of forcefully dislocating the twelfth rib upward provides enough exposure.

In case 5 the abscess was limited to the right extraperitoneal space posterior to the liver and above the level of the twelfth rib. The subcostal approach was made, and the inferior surface of the liver was palpated without opening the peritoneum or locating the high-lying abscess. The edges of the skin and muscles were then retracted higher up, and the twelfth rib was resected. The lower edge of the abscess, which contained 500 cc. of pus, was opened posterior to the liver in the bed of the resected twelfth rib and drained with two large rubber tubes (fig. 4).

In reviewing the operative procedures in my cases, 3 of the 4 abscesses of the superior anterior space were easily drained through the extrapleural portion of the diaphragm by the anterior transcostal operation. In the fourth case the pleural cavity was satisfactorily excluded, and extrapleural drainage was established by an original procedure.

Resection of the twelfth rib by the posterior route was necessary in case 5, in which the abscess was in the right extraperitoneal space.

In case 9 the peritoneal cavity was opened anteriorly.

In 3 cases an abscess of the posterior superior space pointed in the loin, and drainage was done posteriorly beneath the twelfth rib.

CONCLUSIONS

1. One should make every effort to diagnose a subphrenic abscess from the first symptoms, especially when the patient fails to improve satisfactorily after an attack of appendicitis, a perforated ulcer or any abdominal infection or operation.

The onset of symptoms is usually within a week or ten days after the original infection but may develop weeks or months later. Repeated comparative examinations may be necessary for diagnosis.

A quiescent period may precede the onset of symptoms, but no time should be lost before establishing drainage, because the sudden development of sepsis and pulmonary complications is the major factor in the high mortality.

2. Complications may be largely avoided by early drainage with the method most suitable to the location and size of the abscess.

3. An original transcostal operation is reported by means of which immediate extrapleural transcostal drainage may be established.

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INJECTION OF ETHER INTO THE BILIARY TRACT AS TREATMENT FOR CHOLEDOCHOLITHIASIS

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In recent years great strides have been made in the study of the chemistry and physiology of the biliary tract. This increase in knowledge, however, has not altered the position pathologic conditions of the biliary tract hold as formidable opponents of the surgeon's diagnostic and technical skill. In reviewing causes for some of the unsatisfactory surgical results, we find stones in the common duct to be one of the most frequent offenders. The simple case of a large stone high in the common duct, with a typical history of obstruction of the biliary tract, of course, offers no difficulty. However, the small stones low in the common duct frequently remain undiagnosed before and even during operation. Many observers have called attention to the symptomatic silence of this condition. Clute,[1] in reviewing seventy-nine cases of stones in the common duct, found that there was no history of jaundice in twenty-nine. Lahey[2] found that in 39 per cent of his cases of stones of either the common or the hepatic ducts there was absence of jaundice; he called particular attention to the frequency with which small stones low in the duct were overlooked at operation. From time to time many articles have appeared advocating different procedures or instruments for discovering and removing these stones. Nevertheless, in this regard the surgical world is still far from Utopia, and the present status was aptly described by Clute and Swinton[3] when they stated that "as yet we have no means at our command which will determine positively after exploration of the common duct that every stone has been removed." Besides failing to guarantee removal of the stones, exploration of the common duct definitely increases the mor-

From the David May Surgical Research Fund of the Jewish Hospital, and the Surgical Department of Washington University School of Medicine.

1. Clute, H. M.: Common Duct Stones Without Jaundice, S. Clin. North America **11**:261-269 (April) 1931.

2. Lahey, F. H.: Incidence and Management of Stones in Common and Hepatic Ducts, Ann. Surg. **98**:644-649 (Oct.) 1933.

3. Clute, H. M., and Swinton, N. W.: Exploration of Common Duct in Gall-Stone Surgery, Surg., Gynec. & Obst. **59**:906-912 (Dec.) 1934.

tality for operations on the biliary tract. Consequently, any method which would obviate this procedure and still lead to the removal of the stone could be counted as a distinct advance.

Since the discovery by Vollisnieri [4] in 1722 that gallstones were soluble in alcohol and turpentine, innumerable ideas have been presented for the use of lipoid solvents in the treatment of biliary stones. Many years ago (1908) Wright [5] reported a case in which stones were impacted into a mass in the common duct and could be removed only after the injection of 1 drachm (3.7 cc.) of turpentine directly on the impaction. In 1932 Pribram [6] reported a case of cholodocholithiasis, in which the stone was tightly lodged in the papilla of Vater, with successful treatment by the daily injection of ether into the common duct. Later (1935) he [7] reported five cases of "sepsis and cholemia" in which stones in the common duct were also successfully treated by his method, which consisted of the insertion of a tube into the common duct down to the obstruction and the daily injection of "several cubic centimeters of ether" on the stones. In addition to the ether, he mentioned irrigations with sodium chlorate. From time to time he checked the progress of the obstruction fluoroscopically after the injection of iodized oil into the common duct.

The purpose of our work was, first, to investigate the effects of ether, a lipoid solvent, as injected directly into the biliary tract with obstruction of the common duct and, second, to determine whether or not ether would dissolve the ordinary stones under conditions simulating incarceration in and blockage of the common duct.[8]

EXPERIMENTAL METHODS

Mongrel dogs weighing from 15 to 17 Kg. were used in this work. With an animal under ether anesthesia, we tied the common bile duct with two silk sutures as closely as possible to the duodenal wall and cut the duct between the sutures. The head of a small mushroom catheter was fixed into the gallbladder by means of a purse-string suture, the free end of the catheter being brought out of the abdomen by means of a stab wound. The catheter was allowed to drain continuously into voluminous sterile dressings. Several days postoperatively, when the dog appeared and acted normally, the daily injection of from 3 to 6 cc. of ether into the catheter was begun. The only pressure exerted on the ether during the injections was

4. Vollisnieri, cited by Sherwood, K. K.: Historical Sketch of Cholelithiasis, Northwest Med. **30**:335-340 (July) 1931.

5. Wright, G.: The Value of Turpentine in Gall-Stone Surgery, Brit. M. J. **2**:1808, 1908.

6. Pribram, B. O.: Zur Beseitigung eingeklemmter Choledochuspapillensteine, Deutsche med. Wchnschr. **58**:1167-1169 (July 22) 1932.

7. Pribram, B. O.: New Methods in Gall-Stone Surgery, Surg., Gynec. & Obst. **60**:55-64 (Jan.) 1935.

8. We were unable to dissolve the most ordinary bilirubin calcium stones rapidly by mixing them with ether, as described by Pribram. The process usually took a period of days.

that minimal amount necessary to expel the fluid from the glass syringes used for the instillations. Sterile technic was used at all times. While this method of injection was being studied, we noticed marked decreases in the total output of bile. After much difficulty, a satisfactory method was evolved for studying the output of bile, which at the same time permitted us to make the necessary injections. Here, too, the common duct was doubly tied and severed in the foregoing manner. For drainage we used a 10 cm. glass tube with a 1.5 cm. open bulb at each end. One bulbous tip was inserted into the gallbladder and held in place by a purse-string suture. The other end was brought to the outside by forcing it through a small stab wound in the wall of the right side of the abdomen. The external bulbous tip of the tube was sufficient to prevent it from being drawn into the abdomen by respiratory or other movements. The tubing within the abdomen was covered with omentum. To the external bulb of the drainage tube was attached one arm of a T tube, and to another arm of the T tube was connected a balloon for collecting the bile. A screw clamp on the remaining arm of the T tube converted the apparatus into a closed system, so that the biliary drainage was collected in the balloon. To empty the balloon the screw clamp was removed from the free arm of the T tube and placed on the arm connected to the glass drainage tube, thus enabling us to express the bile from the balloon without forcing the fluid back into the biliary tree. To instill the ether the clamp was then placed on the arm of the T tube connected to the balloon, and the drug could be injected through the open arm of the T tube into the gallbladder without entering the collecting bag. After the injection the clamp was replaced on the free arm of the T tube and the bile allowed to collect for another twenty-four hours. All of the external collecting apparatus was held in a circular enameled metal cup, which was in turn supported by a binder of stout canvas. Pockets, which exactly fitted the cups, were tailored into the binders, so that when the latter were tightened the edges of the cups made no undue pressure on the dog's abdomen. The whole apparatus was well tolerated by all the dogs and did not seem to interfere with their normal activity. The injections of ether were not started until a normal output of bile had been maintained for three days. Animals which did not fully recover from the operation or those showing any signs of infection were discarded. The usual diet of meat and water was not varied throughout the experiment. The dogs were taken from their cages each day for fifteen minutes of exercise. When an animal died or was killed because of poor condition, a postmortem examination was done, and sections for microscopic study were taken from various parts of the biliary tract and liver. Tissue was also taken from the pancreas, spleen and kidneys.

To determine the solubility of the usual stone in the biliary tract under conditions simulating incarceration within and blockage of the common bile duct, we placed various stones in pieces of rubber tubing so as to just block the lumen of the tube. The piece of tubing containing the stone was then connected to an inverted bottle partially filled with ether. In order to maintain atmospheric pressure within the bottle at all times, a glass U tube was also placed through the stopper with both arms above the level of fluid. The bottle was agitated daily so as to place "new" ether in contact with the stone.

EXPERIMENTAL RESULTS

Ether was injected into the biliary tract in eleven dogs, and in six of these the total daily output of bile was checked as described. All of the dogs objected strenuously to the injections. This reaction usually subsided in from two to four

minutes but on several occasions was prolonged into what seemed to be a convulsive seizure. The increased pressure within the biliary tract, due to evaporation and movement, caused variable amounts of ether to be expelled. In the dogs with the closed system of biliary drainage, the screw clamp was never replaced on the free arm of the T tube until the ether was no longer being expelled. After the injection dressings were applied, and the animals were removed from the boards and allowed to walk. More often than not a dog would be unable to walk normally, assuming a drunken reeling gait. When this reaction occurred, the dog also became nauseated and vomited. This disturbance in walking usually lasted from ten to fifteen minutes, but the nausea and vomiting persisted for from one half to two hours. Once the injections began, all of the dogs became listless, had meager appetites, appeared extremely weak and lost weight.

All of the dogs (six) on which the twenty-four hour output of bile was measured showed a marked decrease after the instillation of ether. The normal output varied from 130 to 160 cc. per twenty-four hours. After only three or four instillations we could collect but 40 to 50 cc. a day. This decrease in the output of bile was progressive, so that in the three dogs which received the greatest number of injections (eight, eleven and fourteen) there was a complete stoppage of biliary secretion. The eight remaining animals either died or were in such poor condition that they were killed with ether before receiving as many as eight injections.

Clinical signs of jaundice were noted in three of the dogs. These were observed in animals which survived longest and which had also ceased to secrete bile.

At autopsy none of the animals had free bile in the peritoneal cavity, though in one a small amount of a blood-tinged serous fluid was found. Grossly the liver appeared normal except in the three dogs exhibiting jaundice. In these the liver was firmer and definitely bile stained on section. In two animals the bulbous tip of the glass tube which had been maintained in the gallbladder was found to be covered with a layer of fine concretions. In one the common bile duct was thought to be definitely thickened. No gross changes were noted in any other portion of the biliary tract or in any of the other abdominal or thoracic viscera.

Microscopically, the ether seemed to cause a progressive destruction of the mucosa lining the biliary tract and gallbladder. At first the columnar cells became edematous and pale staining and had much lighter nuclei than normally. The cytoplasm then became filled with small granules, the nuclei became still lighter staining and finally the cells appeared to disintegrate and slough. The microscopic changes in the liver were definite and in some instances marked but did not seem to be quantitatively related to the amount of ether injected. Likewise, the hepatic pathologic process gave no clue as to the amount of bile secreted nor as to the general condition of the animal.

The hepatic parenchymal cells were for the most part edematous, and the cytoplasm took an abnormally light stain. The nuclei seemed normal except in those cells which had undergone a fine granular degeneration. In these instances the nuclei were pale. In the dog which had received fourteen injections the liver showed scattered areas of complete destruction. All of the sections showed marked engorgement of the capillaries and slight thickening of the arterial walls. The Kupffer cells were numerous and contained phagocytosed granules, the latter being especially marked in the animals which were jaundiced. These microscopic changes in the liver were present diffusely throughout the lobule and did

not seem to vary with proximity to the bile duct or blood vessel. The pathologic process was slightly more marked, however, in the sections taken at or near the hilus than in those taken from the periphery.

Sections of the spleen, pancreas and kidneys were normal in all dogs except one, which showed many hyaline casts in the renal tubules.

Attempts to dissolve stones placed in rubber tubing in the manner described were unsuccessful after fifteen days of constant contact with the ether. One stone was left in place for three months without leakage of ether past the site of incarceration and obstruction.

COMMENT

The most interesting and noteworthy result of these experiments was the rapid decline of the dogs immediately after the beginning of the injections of ether. The sudden decrease in the total output of bile can be accounted for only by injury to the liver parenchyma, it being conceded that the hepatic cell is the source of bile salt formation. This result, however, is not unusual, for Whipple and Smith [9] found that when small amounts of chloroform, another lipoid solvent, were administered by mouth a "marked depression in the bile salt output" resulted. Thus one would expect an even greater decrease in the total output of bile when, as in the present experiment, the toxic material came in direct and immediate contact with the liver parenchyma. That the injected ether actually did enter the hepatic biliary tree was deduced from the fact that from 3 to 5 cc. of a suspension of barium sulfate injected into the drainage tube was seen to spread up into the liver.

The convulsive seizures, rapid loss of weight and extreme listlessness of the animals point to another expected result, namely, a disturbance in glycogenesis, one of the major functions of the liver. King [10] called attention to the frequent reports of convulsions under ether anesthesia which have appeared in English literature since 1925. Sears [11] expressed the belief that this reaction is a result of hypoglycemia due to a depleted reserve of glycogen and has advocated as treatment the intravenous administration of concentrated solutions of dextrose. Evans, Tsai and Young,[12] working with cats, found that ether anesthesia lowers the glycogen content of the liver from 15 to 20 per cent in from five to six minutes, with a subsequent drop to less than 50 per cent in one hour, after which the fall is checked. Even though ether anesthesia is accompanied by hyperglycemia, which Can-

9. Whipple, G. H., and Smith, H. P.: Bile Salt Metabolism: Liver Injury and Liver Stimulation, J. Biol. Chem. **89**:727-738 (Dec.) 1930.

10. King, H. J.: Convulsions Under Ether Anesthesia, Am. J. Surg. **30**: 182-184 (Oct.) 1935.

11. Sears, J. B.: Late Ether Convulsions: Report of Two Cases, J. A. M. A. **100**:1150-1152 (April 15) 1933.

12. Evans, C. L.; Tsai, C., and Young, F. G.: Behaviour of Liver Glycogen in Experimental Animals; Methods: Effect of Ether and Amytal, J. Physiol. **73**: 67-80 (Sept.) 1931.

tarow and Gehret [13] stated they believed to be due to an increased hepatic glycogenolysis, Major and Bollman [14] found that prolonging such anesthesia caused a marked decrease in the skeletal glycogen. Unfortunately no studies on the chemistry of the blood or tissue glycogen were done in this work. Also interesting would have been a quantitative analysis of the amount of ether present in the various tissues and a comparison of the results with those of Gettler and Siegel,[15] who found that the ether in tissues is "always higher than 0.3 cc. in 500 Gm." in cases in which the patient died under full ether anesthesia or as the result of an accidental overdose. However, as explained previously, histologic evidence of damage due to ether in the spleen, pancreas or kidneys was entirely lacking except in one dog, which showed several hyaline casts within the kidney tubules.

The development of jaundice in three of our dogs was in keeping with the same findings after the administration of other lipoid solvent hepatic toxins, such as chloroform and carbon tetrachloride. The cause of this jaundice, as suggested by Mann and Bollman,[16] "appears to be due in part to hepatic injury and in part to excessive formation of bilirubin which cannot all be eliminated by the injured liver." As mentioned before, the phagocytosis of the excess pigment by the Kupffer cells was especially marked in the jaundiced dogs.

Owing, no doubt, to the relatively short period of observation, sections of the liver failed to reveal other pathologic changes, such as fatty degeneration, cirrhosis or regeneration.

The essential pathologic changes in the extrahepatic biliary tract and the larger bile ducts in the liver were those of necrosis and sloughing of the epithelial lining. There was a noted absence of any inflammatory changes, with only an occasional submucous infiltration of small round cells. Here again the short period of observation precluded the possibility of regeneration of this destroyed mucosa. Under favorable conditions the epithelium lining the ducts is capable of regeneration,[17] and in cats Stewart and Lieber [18] found that ligation of the

13. Cantarow, A., and Gehret, A. M.: Ether Hyperglycemia, with Especial Reference to Hepatic Disease, J. A. M. A. **96**:939-941 (March 21) 1931.

14. Major, S. G., and Bollman, J. L.: Effect of Ether and Iso-Amyl-Ethyl Barbiturate (Amytal) Anesthesia on Glycogen Content of Skeletal Muscle, Proc. Soc. Exper. Biol. & Med. **29**:1109-1111 (June) 1932.

15. Gettler, A. O., and Siegel, H.: Isolation of Ether from Human Tissues, Arch. Path. **17**:510-515 (April) 1934.

16. Mann, F. C., and Bollman, J. L.: Jaundice: Review of Some Experimental Investigations, J. A. M. A. **104**:371-374 (Feb. 2) 1935.

17. Halperin, G.: Regenerative Capacity of the Extrahepatic Biliary Tracts, Surg., Gynec. & Obst. **56**:868-883 (May) 1933.

18. Stewart, H. L., and Lieber, M. M.: Ligation of Common Bile Duct in Cat, Arch. Path. **19**:34-36 (Jan.) 1935.

common duct caused an enormous proliferation of the mucosa of the larger ducts, particularly after the tenth day.

The almost immediate distress of the animals after the injection of the ether was due partially, we think, to the irritating character of the substance and probably more to the rise in pressure within the biliary tract resulting from the evaporation of the ether at body temperature. Pribram [6] warned against the injection of more than 2 to 3 cc. at a time, stating that larger quantities produced pain. Zollinger [19] distended the common duct in man by means of a balloon inserted during laparotomy and found that an increase of pressure within the duct led to severe pain, nausea, vomiting and respiratory difficulty. This description accurately portrays the condition of our animals soon after the instillation of ether. Sheldon,[20] when injecting skiodan into the common duct for visualization, noticed that the patient complained of precordial anginal pain when too great pressure was used.

The deposit of calcium on the glass tubes draining the gallbladder is an interesting but common finding. Hospers [21] cited several workers who before the turn of the century reported the deposition of calcium on foreign bodies placed within the gallbladder. This condition may have been due, as is frequently the case in calcification of the wall of the gallbladder,[22] to the mobilization of the calcium by the blood cells, present in this instance as a result of the operative procedures. A more plausible explanation, however, is that the deposition of calcium was due to the continued irritation of a foreign body, the glass tube in this case. Moynihan [23] gave particular credence to this factor in his work dealing with the deposition of a layer of calcium on gallstones. By making roentgenograms of operative specimens, he found that with few exceptions the smaller stones were translucent, but as a stone became larger a thin radiopaque layer of calcium formed on its surface. It was also his opinion that the calcium deposited more rapidly on an impacted stone.

This covering of calcium is, we think, the explanation of our inability to dissolve an apparently soluble stone by placing it in constant contact with ether as described before. Though solitary stones have

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19. Zollinger, R.: Observations Following Distension of Gall-Bladder and Common Duct in Man, Proc. Soc. Exper. Biol. & Med. **30**:1260-1261 (June) 1933.

20. Sheldon, L. B.: Clinical Study of Biliary Secretion in Case Presenting Completely Obstructed Common Duct, J. A. M. A. **104**:915-916 (March 16) 1935.

21. Hospers, C. A.: Experimental Production of Gall-Stones, with Review of Literature, Arch. Path. **14**:66-78 (July) 1932.

22. Davis, J. E., and Bookmyer, R. H.: Intramural Calcification of Gall-Bladder, Ann. Surg. **96**:413-417 (Sept.) 1932.

23. Moynihan, B.: Mitchell Banks Memorial Lecture on Gallbladder and Its Infections, Brit. M. J. **1**:1-6 (Jan. 7) 1928.

been found to contain from 98 to 99 per cent cholesterol, the common mixed or combination gallstones were found to have an average cholesterol content of but 94 per cent.[24] Thus while the calcium content is relatively small, its position as an enveloping layer may easily be sufficient to prevent solution of the stones by lipoid solvents.

Thus far we have discussed features concerning this method of treatment as brought to light by our experimental work. There are other points to bear in mind before injecting a lipoid solvent into the biliary tract. Ever since Graham [25] first described it, the occurrence of hepatitis has been accepted as a "constant accompaniment of cholecystitis." Since we also think of stones as evidence of an antecedent disturbance of the gallbladder or the liver,[26] in any case in which surgical intervention for stones is necessary there is, or has been, infection of the liver, and there may be a more dangerous reaction to a toxic agent than is expected or is desired.

Another theoretical consideration is the possibility of the ether causing pancreatitis. That this is commonly possible mechanically was demonstrated by Cameron and Noble [27] on postmortem experimentation. They inserted 3 mm. calculi into the terminal portion of the choledochus and raised the intraductal pressure to 100 mm. of water. It was found that fluid entered the pancreatic duct in sixty-six of one hundred cases, and in seventy-four of the one hundred there was an ampullary communication between the choledochus and the duct of Wirsung. They also called attention to the fact that during retching or vomiting the pressure within the common duct usually rose to 350 mm. of bile, but might go as high as 1,000 mm. These findings are in striking accord with those of Wangensteen and his co-workers,[28] who reported that in 69.8 per cent of their cases of acute pancreatitis the condition was associated with stones or disease of the gallbladder. Since in our experiment the common duct was severed just outside the duodenum, we were unable to check these findings.

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24. Pickens, M.; Spanner, G. O., and Bauman, L.: Composition of Gall-Stones and Their Solubility in Dog Bile, J. Biol. Chem. **95**:505-507 (March) 1932.

25. Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521-537 (May) 1918.

26. Bortz, E. L.: Restoration of Biliary Function, M. J. & Rec. **136**:244-248 (Sept. 21) 1932.

27. Cameron, A. L., and Noble, J. F.: Reflux of Bile up the Duct of Wirsung Caused by an Impacted Biliary Calculus, J. A. M. A. **82**:1410-1414 (May 3) 1924.

28. Wangensteen, O. H.; Leven, N. L., and Manson, M. H.: Acute Pancreatitis (Pancreatic Necrosis): Experimental and Clinical Study, with Special Reference to Significance of Biliary Tract Factor, Arch. Surg. **23**:47-73 (July) 1931.

While the experimental evidence and conjectural possibilities offered here may present this method of treatment as a rather perilous one, it must be pointed out that our experimental procedures were not identical with the therapeutic ones advocated by Pribram. For example, we injected the ether into the gallbladder instead of into the choledochus. This probably permitted more ether to remain within the biliary tract. Likewise, our injections of ether were not followed by irrigations with sodium chlorate, which would remove some of the residual ether. Then, too, the amount of ether used in the dogs (from 3 to 6 cc.) was a relatively much larger dose than a similar amount in human beings. We might also mention that we made no effort to prolong the period of survival of the animals by the administration of carbohydrates, a much needed substance in cases of damage to the liver.

While these exceptions may explain the toxicologic toleration of this type of treatment by man, they do not account for Pribram's success in overcoming lithoid obstructions of the choledochus by lavage with ether. Of course, it is entirely possible that all of his cases were those in which the stones were composed of pure cholesterol or at least were not covered with a layer of calcium and were, therefore, readily dissolved by the ether. Then, too, the lavage may have been instrumental in overcoming spasms of the sphincter of Oddi, which may in contracture resist pressures much higher than either the secreting pressure of the liver or the expulsive pressure of the gallbladder.[29] A more likely explanation, however, is that the mechanical effects of the injections of ether, sodium chlorate or iodized oil were sufficient to dislodge and remove the cause of the occlusion. Frequent reports of similar experiences have appeared in the literature. For example, about twenty-five years ago Matas [30] was "surprised" by the rapid cure of biliary fistulas after catheterization of and injection of fluids into the biliary tract. Neuwirt,[31] after the injection of 15 cc. of iodized oil into a biliary fistula for visualization, discovered that stones were passed with the stool and via the fistula onto the abdominal wall. More recently, Hicken, Best and Hunt [32] summarized their experiences with the statement that "occasionally a lipoiodine [iodized oil] lavage of the common

29. Ivy, A. C., and Bergh, G. S.: Applied Physiology of Extrahepatic Biliary Tract, J. A. M. A. **103**:1500-1504 (Nov. 17) 1934.

30. Matas, R.: Catheterization of the Common Duct as a Practical and Effective Upper Route for Enteroclysis Medication in Toxic Biliary Cases (McArthur's Procedure), Surg., Gynec. & Obst. **12**:185-186, 1911.

31. Neuwirt, K.: Therapeutische Wirkung einer Ölfüllung der Gallenwege, Zentralbl. f. Chir. **57**:1663-1665 (July 5) 1930.

32. Hicken, N. F.; Best, R. R., and Hunt, H. B.: Cholangiography: Visualization of the Gallbladder and Bile Ducts During and After Operation, Ann. Surg. **103**:210-229 (Feb.) 1936.

duct will flush out small stones or inspissated plugs of mucus which are causing distress and discomfort in cholecystectomized patients, or perhaps release the sphincterismus."

In conclusion, we can recommend only as thorough as possible surgical removal of the stones in the common duct. If obstruction of the choledochus develops, an injection of the inert iodized oil may be of value not only in visualizing the biliary tract but in the release of the obstruction.

SUMMARY

A closed system for the collection of bile from, and the injection of materials into, the biliary tract is described.

The experimental and theoretical results of direct injection of ether into the biliary tract are discussed.

Attempts to dissolve the usual cholesterol stones in ether are described and dissolved.

Pribram's method is discussed.

CONCLUSIONS

Ether may be very toxic when injected directly into the biliary tract.

The thin layer of calcium so frequently present around a cholesterol stone will prevent the ready solution of the stone by ether.

Lavage of the biliary tract with iodized oil is suggested for removing obstructions of the common duct as well as for visualization.

CARCINOMA OF THE INFRAPAPILLARY PORTION OF THE DUODENUM

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PHILADELPHIA

The purpose of this communication is to report two new cases of carcinoma of the infrapapillary portion of the duodenum and to review and analyze the previously reported authentic cases of this condition. Of sixty-two cases reported, twenty-eight were regarded as satisfactory,[1] a clinical history and gross and microscopic descriptions of the tumor, obtained at laparotomy or at postmortem examination, being presented in each report. Eight[2] additional cases, although probably authentic examples of this condition, were not included because the reported data were insufficient for our purposes. Twenty-four cases[3] were discarded because the reports lacked a histologic description, and in two others[4] the exact situation of the tumor was uncertain.

The first reported example of a carcinoma of the infrapapillary portion of the duodenum is usually accredited to Chomel (1852), but the case described by Irwin in 1824 is probably a genuine example of this condition and should take precedence. Since the journal in which this paper was published is not readily accessible, a brief abstract is presented. The patient was extremely emaciated and complained of pain in the epigastrium, which was excruciating at times and was usually

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From the Pathological Laboratories of the Jefferson Medical College and Hospital, the Jefferson Hospital Tumor Clinic and the Philadelphia General Hospital.

1. Déscroizelle; Baillet; Rolleston; Fenwick; Schiewe; Syme; Thaysen; Head; Cade and Devic; Deaver and Ravdin; Vickers; Lundberg; Pommay and Seille; Pauchet and Luquet; Dewis and Morse (cases 7 and 12); Ylvisaker; Schofield; Forni; Meyer and Rosenberg (cases 3 and 4); Mateer and Hartman (case 6); Kellogg; Fariñas Mayo; Sala; Harries and Harrison (case 2); Eger (case 2); Laning and Loy (case 2), and Davis.

2. Larkin; Geiser (case 7); Venot; Markus; Borrmann (case 3); Raiford (cases 44556 and 46153), and Price (case HB 7008).

3. Irwin; Chomel; Williams; Markoe; Whittier (case 13); Herz; Geiser (cases 5, 6 and 8); Bland-Sutton; Erdmann; Crane (case 1); Eusterman, Berkman and Swan (cases 13, 14 and 15); Dewis and Morse (cases 10 and 11); Susman (case 3); Surmont and Tiprez; Rankin and Mayo; Eger (case 2); Lengemann; Joyce (case 8), and Auvynet.

4. Bandelier (case 6) and Goldberg (case 2).

accompanied by vomiting of a green fluid from two to four hours after meals, obstinate constipation and black feces. About three weeks before death a large tumor was discovered in the right side of the hypochondrium; the prominence was present for from eight to ten days and then subsided. The autopsy report is as follows:

On exposure of the abdominal cavity, the stomach was seen displaced in a singular manner, and enormously distended. This organ occupied almost the whole of the right hypochondrium—its great curvature extending down to the left iliac region. After its removal from the body, it was opened and its contents were found to amount to half a gallon of green bile, somewhat diluted with whiskey and water, which had been taken for common drink. It was then slit from one extremity to the other, carefully washed, and contrary to the opinion I had formed of its condition, not a vestige of disease was to be discovered in any part of this organ. The liver, also, was free from disease, but adherent on its posterior surface—gallbladder much distended with thin green bile. Having examined thus far without being able to detect the seat of the disease, our attention was directed to the duodenum, which was found much enlarged, and externally hard and unyielding. On exposing its cavity, it was found in a cancerous state, and closely studded with tubercles, varying in size from a hickory nut to that of a hazel nut. The largest of them contained matter resembling cream somewhat dried. The whole surface of the seat of ulceration presented a ragged, uneven, lacerated appearance. The quantity of pus found about the diseased part of the gut was upwards of a gill. Pancreas natural in regard to situation, but diminished to one half its usual size and scirrhous. On cutting into it, the interior presented much similarity in colour and texture to that of a boiled cow's udder. Duct natural. . . . The mesenteric glands enlarged—and between the lamina of the mesocolon were contained several tumours of about the size of a large pea, in a state approaching to scirrhous. . . .

The reports of two new cases of carcinoma of the infrapapillary portion of the duodenum follow:

REPORT OF CASES

Case 1.—R. R., a white man aged 52, was admitted to the Jefferson Hospital on Aug. 28, 1933, with a loss of 30 pounds (13.6 Kg.) in weight and persistent pain in the region of the gallbladder of two months' duration, which suddenly became excruciating two weeks previously. The pain appeared to originate in the right flank posteriorly and radiated along the right costal margin to the area of the gallbladder and occasionally to the region of the right scapula. It was unaffected by the ingestion of fried or fatty foods or sodium bicarbonate. There were associated belching, nausea, vomiting, hiccups and a feeling of fulness and discomfort in the right upper abdominal quadrant. Obstipation developed a week after the acute onset; the urine became dark, and the stools were either black or acholic. Jaundice was first noted by the examining physician. The liver was enlarged and tender, and the abdomen was somewhat distended and rigid on light palpation over the right upper quadrant. When the examiner's thumb was pressed under the right costal margin, the patient would catch his breath on deep inspiration.

Roentgenographic examination of the stomach and intestines was unsatisfactory. No gallbladder shadow was observed after the oral administration of a mixture of tetra-iodophenolphthalein sodium and tartaric acid. The urine contained albumin

and bile pigments but no bile salts. The stools were acholic but later became dark and contained blood and sometimes fat. Repeated drainage of the biliary tract yielded little if any bile. Analysis of the gastric contents after a test meal showed a maximum total acidity of 113 at the end of thirty minutes and a maximum of free hydrochloric acid of 100 at the end of forty-five minutes; lactic acid and bile were absent, and blood was present in all specimens. The Kahn and Wassermann reactions of the blood serum were plus four. The red blood cell count dropped from 4,320,000 on the patient's admission to 2,300,000; the number of platelets increased steadily from 572,000 to 1,055,000. The nonprotein nitrogen content of the blood rose from 38.96 to 90.88 mg. per hundred cubic centimeters of blood; the creatinine content was 1.65 mg., and the cholesterol content, 156 mg. On his admission the reaction to the direct van den Bergh test was positive; the serum bilirubin was 4.2 mg., and 45 per cent of bromsulphalein was retained at the end of thirty minute periods (2 mg. dose). On the day that death occurred the van den Bergh reaction had not changed; the serum bilirubin was 17.45 mg., and 100 per cent of the bromsulphalein was retained. Death occurred on October 3.

Autopsy was performed thirteen hours after death. The combined gross anatomic and microscopic diagnoses were (1) adenocarcinoma of the duodenum, with extension to the pancreas and metastasis to the regional lymph nodes, liver and lungs; (2) hydrohepatosis with marked jaundice; (3) chronic aortitis; (4) arteriosclerosis of the coronary arteries; (5) fatty infiltration of the myocardium, and (6) calcified tuberculous lesions in the lungs.

The posterior wall of the duodenum presented a sharply defined firm round elevated lesion, 3.5 cm. in diameter, which involved the mucous membrane covering slightly more than half the circumference of the intestine. The proximal margin of the lesion occupied a position 13.5 cm. distal to the pylorus and 2.5 cm. beyond the papilla of Vater. The wall of the intestine in the area of involvement was composed of soft gray, homogeneous tissue. This tissue penetrated deeply into the pancreas and more superficially extended beneath the mucous membrane to the margin of the ampulla of Vater. Many of the regional lymph nodes were enlarged and replaced by soft gray, homogeneous tissue adherent to the pancreas and the duodenum. The proximal portion of the duodenum and the stomach and esophagus were markedly distended with fluid and gas. Several small shallow diverticuli were observed on the posterior wall of the duodenum just below the pylorus.

The papilla of Vater was thickened and indurated and appeared more prominent than usual. The ampulla received the duct of Wirsung and the common bile duct, both of which were obstructed. The duct of Santorini opened directly into the duodenum at a point slightly anterior to and 2.5 cm. above the papilla of Vater; it was large and appeared to be continuous with the main pancreatic duct within the body of the pancreas. All the biliary passages were markedly dilated and stained with bile. Obstruction of the biliary tract seemed to result from a combination of neoplastic infiltration of the wall of the ampulla of Vater and from external pressure of the tumor tissue in the duodenum and pancreas and the enlarged lymph nodes in the retroperitoneal space. The wall of the gallbladder was somewhat thickened, and the fundus extended several centimeters below the inferior border of the liver. The liver was enlarged, somewhat cystic and mottled dark green. On section there were innumerable sharply circumscribed gray tumor nodules scattered throughout the parenchyma, the largest of which measured from 4 to 6 cm. in diameter.

Microscopic sections of the duodenum passed through a large tumor nodule, the base of which rested on the muscular coat of the intestine (fig. 1). The epi-

thelial cells extended downward from the mucosal nodule and spread out laterally into the submucosa and in one place penetrated deeply through the muscular wall into the subserous tissue. At the summit of the nodule the duodenal mucosa became atrophic and merged into atypical epithelial cells, loosely distributed and supported by a scant stroma, which formed the core of several tall, villus-like structures. The blood vessels of the stroma were often thin and immature. The atypical epithelial cells were round, oval or polyhedral, with smooth acidophilic or pale foamy cytoplasm. The nuclei were hyperchromatic or pale, vesicular, small or large, often crescentric, lobulated and eccentrically placed in the cell. As a rule they were single, but many individual cells contained from two to ten nuclei. There were a few bluish interlacing strands among these epithelial cells, suggesting

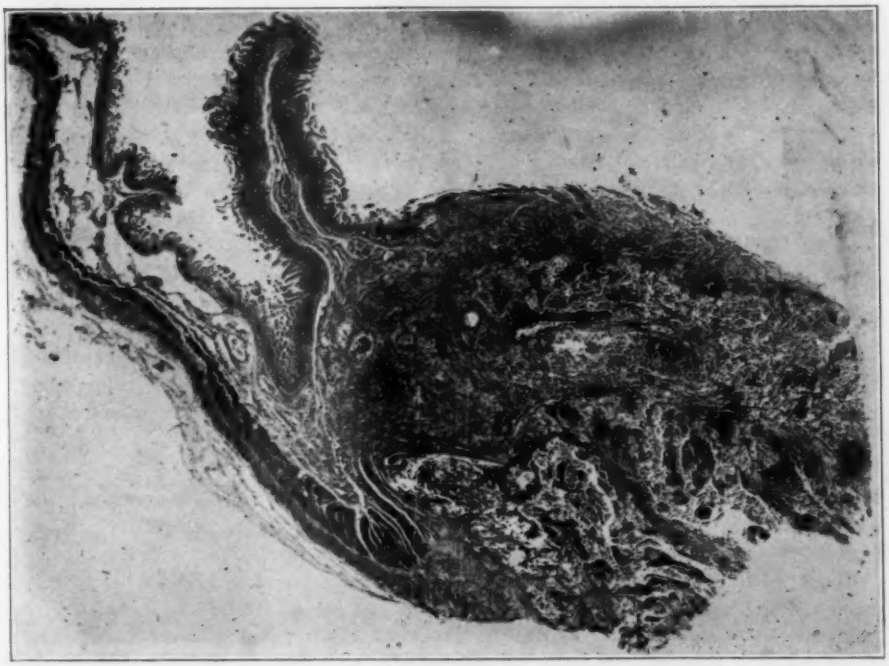

Fig. 1.—Microscopic section of the duodenum at the margin of the tumor, showing infiltration and destruction of all the coats of the intestine; circa × 7.

the presence of mucin. Scattered through the nodule were a number of polymorphonuclear leukocytes, usually in association with necrotic areas, which were numerous in the sections. There were many collections of round cells and a few polymorphonuclear leukocytes in the deeper layers of the musculature. The metastatic lesions in the lung and liver resembled the primary nodule in the duodenum. There were several large neoplastic nodules lying in relation to some of the ducts in the pancreas, which showed a moderate degree of fibrosis about the smaller ducts. In this situation, as in the metastatic lesions of several of the lymph nodes, the atypical epithelial cells were paler; they tended to form better developed acini and contained more mucin than the primary duodenal nodule. Several areas of tumor tissue were observed in and about small thin-walled vessels outside the capsules of some of the lymph nodes.

The hepatic parenchyma presented the characteristic picture of biliary stasis, with necrosis and pigmentation about the central veins, proliferation of the smaller bile ducts, marked perilobular fibrosis and round cell infiltration and a few lesions of biliary necrosis.

CASE 2.—P. S., a Negress aged 51, under treatment for diabetes and hypertension of at least a year's duration, was admitted to the Philadelphia General Hospital on Oct. 23, 1933, with nausea, vomiting, abdominal pain, diarrhea and constipation. The onset occurred suddenly ten days previously, with steady epigastric pain, which became worse on eating, and diarrhea. This was succeeded by obstinate constipation and vomiting of clear liquid and recently ingested food. On physical examination the skin was dry, and the breath smelled of acetone. Three liters of foul-smelling fluid was siphoned off through a stomach tube. Roentgenographic examination of the gastro-intestinal tract after the ingestion of a barium sulfate meal disclosed a dilated, atonic stomach, which had a persistent filling defect on the greater curvature of the pylorus. The duodenal cap was well outlined and seemed perfect, but beyond this point little barium sulfate was observed to pass, which gave a slightly granular appearance to the remainder of the duodenum. The lower portion of the intestinal canal seemed normal after a barium enema. There was no anemia; the chloride content of the blood was 584 mg. per hundred cubic centimeters; the sugar content varied between 130 and 234 mg., and the Kahn reaction of the blood serum was negative. The urine contained a faint trace of albumin and had a specific gravity of from 1.015 to 1.039.

At laparotomy, on November 11, a firm nodular constriction was found which was thought to be a tumor of the pylorus, and gastro-enterostomy was performed for relief of obstruction. On the sixth postoperative day a suppurative lesion developed in the right parotid gland, which was incised and drained on November 20. A sinus tract formed and later ruptured into the right external auditory canal, resulting in paralysis of the right side of the face. The patient died on December 9 from an infection of the blood stream.

Autopsy was performed nine hours after death. The combined gross anatomic and histologic diagnoses were: (1) adenocarcinoma of the infrapapillary portion of the duodenum, with extension to the pancreas and metastasis to the liver; (2) marked dilatation of the proximal portion of the duodenum; (3) a patent gastro-enterostomy opening; (4) abscesses of the right parotid gland and kidney; (5) arteriosclerosis of the aorta and the renal, coronary and pancreaticoduodenal arteries; (6) acute degeneration of the myocardium and renal tubular epithelium; (7) congestion of the lungs, spleen and liver; (8) interstitial fibrosis of the pancreas, and (9) fatty change of the liver.

About 11 cm. from the pylorus the duodenum presented an annular constriction 3 cm. in diameter, with a lumen which barely permitted the passage of a fine probe. The wall of the duodenum at the point of involvement was composed of firm white tissue, which infiltrated the head of the pancreas. The proximal portion of the duodenum was markedly dilated. The common bile duct was patent, slightly thickened and measured 1.5 cm. in diameter; bile could be expressed through the ampulla of Vater, which lay 1 cm. proximal to the duodenal lesion. No metastatic nodules were observed in the abdominal lymph nodes.

Microscopic sections through the lesion included the duodenum and an adjacent portion of the pancreas (fig. 2). The strip of mucous membrane terminated abruptly at either end and did not show a transition laterally into malignant tissue. In the deeper layers of the mucosa and muscularis mucosa were several nodules of atypical cells with pink cytoplasm and hyperchromatic nuclei, frequently with large

multiple lobulations and numerous mitotic figures. The cells around the periphery of these nodules tended to form columnar rows resembling the cells in the depths of the duodenal crypts. The entire submucosa was invaded by nests and strands of tall columnar vacuolated cells, which occasionally formed elongated acini and closely packed cellular nests. They penetrated through the muscular coats into the septums of the pancreas for a short distance. The stroma was moderate in amount and infiltrated with small round cells.

The liver showed metastatic lesions, acute congestion, central lobular cytoplastic vacuolation and a moderate degree of periportal round cell infiltration. The kidney was intensely congested and contained a focus of early suppuration in the medulla.

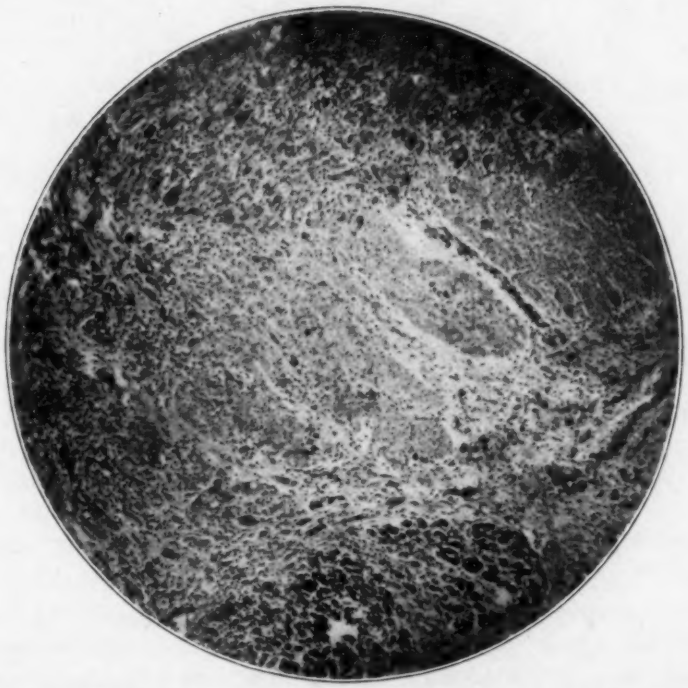

Fig. 2.—Microscopic section of the wall of the duodenum just beneath the ulcerated area. There were atypical epithelial cells in the submucosa, which permeated through the muscular coats into the septums of a small portion of the pancreas attached to the deeper portion of the section; × 40.

AGE AND SEX; INCIDENCE

In the series of cases studied the patients consisted of twenty men ranging in age from 40 to 74 years, with an average age of 58.2 years, and ten women (two Negresses) ranging in age from 35 to 61 years, with an average age of 48.3 years.

Carcinoma arising in the duodenum is estimated to be found in from 0.01 to 0.1 per cent of all postmortem examinations. The per-

centages commonly given range from 0.01 to 0.03 (Eusterman and Balfour). Nearly one half of the malignant growths of the small intestine are said to develop in the duodenum (Kellogg), but these statistics are based on reports in the literature, and many of these are not authentic cases. Of the two new cases here reported, one was found at the Jefferson Medical College Hospital in a series of 3,526 autopsies and the other at the Philadelphia General Hospital in a series of 20,176 autopsies performed since 1920.

ANATOMY

Textbooks on anatomy usually state that the duodenum is divided into the following parts: (1) the superior portion, from 3 to 5 cm. in length, which commences at the pylorus and passes upward and backward, where it forms, with the second portion, the superior flexure; (2) the descending or vertical portion, from 8 to 12 cm. in length, which receives the bile and pancreatic ducts and forms with the third portion the inferior flexure; (3) the inferior portion, which is again subdivided into (*a*) the horizontal portion, from 8.5 to 10 cm. in length, which terminates in (*b*) the ascending portion, from 3 to 7 cm. in length, this in turn terminating in the duodenojejunal flexure.

Any division of the duodenum which fails to take into consideration the point of entrance of the bile and pancreatic ducts is inadequate for clinical purposes. Embryologically, all of the duodenum above the papilla of Vater is developed from the foregut, and the remainder of the small intestine is derived from the yolk sac, or so-called midgut. With the papilla of Vater as an orientating mark for subdivision, that portion of the duodenum above is the suprapapillary segment; that below, the infrapapillary segment.

The infrapapillary portion extends from the papilla of Vater to the duodenojejunal junction. It consists of three subdivisions, which are best seen in the U-shaped duodenum, less well in the C-shaped type and not at all in the V form: 1. The descending portions extend along the right side of the vertebral column from the papilla of Vater to the inferior angle on a level with the upper border of the body of the fourth lumbar vertebra. It is in relation in front with the transverse colon and small intestine and behind with the right kidney in the neighborhood of the hilus, the renal vessels, the inferior vena cava and the psoas muscle. At its medial side are the head of the pancreas and the common bile duct and laterally the right colic flexure. 2. The horizontal portion, from 5 to 7.5 cm. long, begins at the inferior angle, passes from right to left, with a slight inclination upward in front of the great vessels and crura of the diaphragm, and ends in the ascending portion in front of the aorta. It is crossed by the superior mesenteric vessels and the mesentery. Its posterior surface lies on the right crus

of the diaphragm, the inferior vena cava and the aorta, and the upper surface is in relation with the head of the pancreas. 3. The ascending portion, 2.5 cm. long, extends along the left side of the aorta as far upward as the level of the superior border of the second lumbar vertebra, where it turns abruptly forward to end in the duodenojejunal flexure. It lies in front of the left psoas muscle and left renal vessels.

MORBID ANATOMY

The dimensions of the primary tumor in the duodenum were stated in twenty-five cases. In a little over half of these it measured from 3 to 5 cm. in length, in six cases from 1 to 2.5 cm. and in five cases from 6 to 8 cm. In Rolleston's case the infrapapillary segment was involved in its entirety. A circumscribed tumor 4 cm. or less in diameter was localized just beyond the papilla of Vater in eight cases and at or near the duodenojejunal flexure in thirteen. In eight cases the proximal margin of the growth was situated near the papilla of Vater, and the distal margin of the neoplasm did not extend beyond the horizontal portion of the duodenum, except in the extensive growth considered previously. Ulceration was present in sixteen cases. A few ulcers were crater-like, measuring upward of 6 cm. in diameter, with margins variously described as hard, resistant, cicatrized, indurated, friable, rolled or elevated. A gaping artery was present in the floor of one ulcer, and perforation occurred in four.

The primary tumor was completely annular in nineteen cases and was confined to the posterior or the median wall or to both in six. Some degree of stenosis was present in all cases, being complete or almost complete in seventeen. The annular tumors were frequently fixed and consisted of compact grayish white cicatricial-like tissue. The non-annular growths were polypoid or pedunculated and usually soft in consistency.

Proximal to the primary duodenal lesion, the alimentary canal was regularly dilated well up into the esophagus. The proximal portion of the duodenum was frequently distended in a funnel-shaped or pyriform manner, and its mucous membrane was flattened and atrophied or occasionally puckered and thrown into folds, while the muscular coats were usually attenuated but occasionally were thick and hypertrophied. The pyloric sphincter showed marked thinning, and the orifice was dilated, sometimes to a diameter of 12 cm., the stomach and duodenum together often appearing as a bilocular viscus. The gastric contents occasionally measured 1,500 cc. and consisted of degenerated blood and remnants of food. In Schiewe's case the stomach was the size of a "pig's bladder," with the pylorus in the right anterior axillary line and the duodenum the width of a normal colon. Fenwick stated that the

anterior abdominal cavity of his subject was chiefly occupied by two thin-walled sacs lying side by side; the one on the left consisted of a dilated stomach, while the other, which was ovoid and 8 inches (20 cm.) in length with a maximum circumference of 13 inches (33 cm.), represented the upper two thirds of the duodenum. In occasional cases in which the clinical manifestations indicate low grade, long-continued obstruction, the wall of the stomach and proximal portion of the duodenum may become markedly hypertrophied. Rolleston explained this change on the basis that from time to time food collects proximal to the obstruction and, by forcing the duodenum downward, leads to complete closure of this fixed and already strictured portion of the bowel.

Metastases or extension of the primary tumor to adjacent structures occurred in fifteen cases. Metastatic deposits were present in the lymph nodes in ten, in the liver in seven and in the lungs in two. The regional nodes were involved in all ten cases of lymphatic metastases, the mesenteric nodes in four, the retroperitoneal nodes in three and the periportal nodes in three, while in one case practically all the visible nodes in the abdomen and pelvis were affected. Adhesions to the surrounding structures were encountered in half the cases, but which of these were neoplastic could not be accurately estimated. Neoplastic extensions into the pancreas occurred in five cases, and into the surrounding fat, posterior abdominal wall and aorta, in one each. The largest tumorous deposits in the pancreas did not exceed 3 cm. in diameter. The primary and infiltrating tumors together with the cancerous lymph nodes and adhesions sometimes produced a large fixed neoplastic mass, which compressed surrounding tissues and viscera. Obstruction of the terminal end of the common bile duct or the ampulla of Vater occurred in five cases, due in most instances to extension of the primary neoplasm.

Perforation of the duodenum occurred in four cases. Rupture developed spontaneously in Dewis and Morse's case 12, and the resulting lesion was walled off by surrounding tissues. In Pommay and Seille's case, fistulous formation occurred three days after gastroenterostomy and biopsy and resulted in diffuse peritonitis. In Schofield's case perforation occurred after the implantation of radon seeds, which were believed to have interfered with healing of the duodenostomy wound. Perforation in Ylvisaker's case was found fifteen days after incision and drainage of the pancreas and several months after high voltage roentgen therapy over the epigastric region.

Morbid anatomic lesions other than the foregoing were mentioned only rarely. Chronic pancreatitis was observed in six cases, suppurative pancreatitis in one and obstruction of the duct in Wirsung in two. Of five cases in which biliary stasis was present, the hepatic changes

were described in one and resembled those resulting from biliary obstruction due to other causes. Chronic cholecystitis was found in two cases, suppurative cholangeitis in one, pyemia in two and biliary calculi in one. Degenerative changes in the tubular epithelium of the kidney were frequently noted. Inflammatory hyperplasia of the lymph nodes in the upper part of the abdomen was regularly associated with extensive infection in and about the primary duodenal neoplasm.

HISTOLOGIC PICTURE

The lesion was designated as a glandular carcinoma in all cases, but aside from this statement microscopic data were scanty. Biopsy material or the entire surgical specimen was obtained for examination by laparotomy in nine cases. The growth was of the scirrhous type in seven cases, the medullary type in four and the mixed scirrhous and medullary type in two. Papillary formations were marked in five cases, and variable amounts of mucin were present in four; in two of these the formation was described as a mucinous adenocarcinoma. Variations from a well differentiated carcinoma of the intestinal type with cylindric cells to one of rather marked anaplasia were described, and in ten cases anaplasia and rapid cellular division were noted. Inflammatory changes were regularly present in the connective tissue stroma and were pronounced in three cases in which ulceration was present.

PATHOLOGIC PHYSIOLOGY

There are relatively few studies of the abnormal physiologic changes associated with clinical obstruction of the infrapapillary segment of the duodenum. In animals, Elman and Hartman concluded that the principal cause of death is a change in the chemical constituents of the blood, resulting primarily from the loss of gastro-intestinal secretions and secondarily from circulatory and renal insufficiency due to dehydration. By introducing a solution of sodium chloride below the point of obstruction, life can be maintained in experimental animals, whereas the reintroduction of bile and pancreatic juices fails (Armour, Brown, Dunlop, Mitchell, Searls and Stewart). Owing to the similarity between the toxic reaction of the material from obstructed loops of bowel and that of histamine, Dragstedt suggested that the latter was formed by the bacterial decomposition of histidine as the result of stasis. He expressed the belief that histamine accelerates the secretogogic action of the intestines and that the excessive secretion in turn facilitates distention and consequent breakdown of the normal resistance of the intestinal mucosa against toxic material in the lumen of the bowel. It is also probable that death is hastened by slow absorption of histamine-like

substances, which are believed to accelerate chemical changes occurring as a result of loss of gastric secretion (Andrus, Guest, Gates and Ashley).

From a clinical point of view the signs and symptoms of obstruction of the type considered in this paper have been divided by Rivers and Thiessen into two groups. In the first are included symptoms arising from local mechanical disturbances or those incident to neoplastic invasion of surrounding tissues. The second group includes systemic disturbances arising as a part of the toxemia associated with obstruction together with the manifestations of malignant cachexia, metastasis and extension. On the basis of previous studies it has been shown that the symptoms resulting from interference with normal peristalsis are flatulence, nausea and regurgitation of food, which may not reach their maximal intensity for an hour or more after eating. Vomiting of the retention type develops, even with incomplete obstruction, and leads to varying degrees of malnutrition and dehydration. At first the stenosis is adequately counteracted by increased peristalsis, but later compensation becomes inadequate, and signs and symptoms of partial or complete obstruction may supervene rapidly. Obstruction by malignant disease is rarely intermittent, and relief is seldom obtained except by surgical measures. Since the lesion is situated below the ampulla of Vater, the vomitus or gastric contents obtained by lavage usually contain bile in liberal amounts, except in occasional instances in which the biliary passages as well as the intestine are obstructed.

CLINICAL FEATURES

Onset.—The onset of the condition was acute in twelve cases, gradual throughout in twelve and first gradual and then acute in six. A history of antecedent illness was elicited in three cases in which the onset was acute and in seven cases in which the course was gradual throughout.

The duration of the condition in eleven cases in which the onset was acute ranged from fourteen days to seven months, averaging slightly less than four months. In one case the patient was not traced after operation and discharge from the hospital. The initial symptoms in this group consisted of epigastric distress or pain (twelve cases), vomiting (ten), loss of weight and strength and anorexia (five), a sense of abdominal weight or pressure (two), belching (two) and constipation, diarrhea, abdominal distention, hiccups and bulimia (one each). Later manifestations included constipation (four), loss of weight and strength and anorexia (four), and jaundice, vomiting, a sense of weight or pressure in the abdomen and abdominal distention (one each).

The duration of the condition in cases in which the course was gradual throughout ranged from five to nineteen months, averaging slightly less than eleven months in nine instances; the ultimate fate of three patients was not stated. Initial symptoms in this group consisted of pain (six cases), vomiting (five), loss of weight and strength (two), abdominal distention (two) and a sense of weight or pressure in the abdomen, belching and diarrhea (one each). Later manifestations were loss of strength and weight and anorexia (eight cases), pain (four), vomiting (four), diarrhea (three), abdominal distention (two) and a sense of weight or pressure in the abdomen and constipation (one each).

In the group in which the course was at first gradual and then acute, the duration of the first stage was approximately ten months and of the second, approximately four and a half months, the average total duration being about eleven months. The gradually developing symptoms included pain (three cases), a sense of weight or abdominal pressure (one) and loss of weight and strength (one). The subsequent acute manifestations were vomiting (five cases) and flatulence, jaundice, abdominal distention, constipation and loss of weight and strength (one each). Still later, there were loss of weight and strength and anorexia (two cases), constipation (two) and pain, jaundice and abdominal distention (one each).

The clinical diagnoses in the cases in which there was an antecedent history were reported as lead poisoning, cholecystitis, neurosyphilis, traumatic rupture of the intestine and arteriosclerosis with diabetes and with hypertension (one case each) and simple ulcer (two). In the remaining three cases the patients complained of symptoms referable to the upper part of the abdomen which were not diagnosed.

Pain.—Pain was present in all but one case and was usually severe and sometimes colicky or cramplike. It was frequently intermittent at first, then increased markedly in severity and eventually became continuous. In a few cases there was simply epigastric distress, slight burning or a feeling of distention and fulness. Pain occurred with the onset in twenty-two cases and later in seven. It was situated in the epigastrium in twenty-one cases, in the right upper abdominal quadrant in three, in the lower part of the abdomen in two and in the right flank posteriorly in one. Radiation to the back occurred in four cases and to the region of the shoulders in two. This symptom occurred from one half to two hours after meals or was aggravated or intensified by food in seventeen cases, while in three cases it was unaffected by food. Relief sometimes followed the ingestion of food, vomiting or lying on the right side, and in one case both pain and meteorism disappeared after the administration of morphine. Attacks of severe pain were

sometimes followed by epigastric burning, discomfort and a sense of weight in the abdomen and in one case these were preceded by hunger and followed by vomiting. There was associated tenderness in eight cases and abdominal rigidity in two.

Vomiting.—Vomiting was present in twenty-five cases, absent in four and not mentioned in one. It appeared with the onset in seventeen and after the onset in eight, usually occurring from a few minutes to several hours after meals. It was at first intermittent and tended to become incessant terminally and was only occasionally associated with nausea. The vomitus was frankly bilious in ten cases, and in three contained coffee-ground material; sometimes food ingested from several hours to several days previously was present, in which case the vomitus often had a foul odor due to putrefactive changes. Some patients had gastric succorrhea, and the amount of fluid vomited exceeded that ingested; in Rolleston's case 11 pints (6.2 liters) was vomited in fifteen hours, and in Fenwick's case 13 ounces (0.4 liter) of bilious fluid was obtained from the stomach, which had been emptied and without food since the previous night. Vomiting occurred at any time of the day or night and was not associated with any particular kind of food. Sometimes, however, the patients vomited at regular intervals, as, for example, after meals, once a day or periodically every second day. Of the four cases in which vomiting was absent (Deaver and Ravdin; Pommay and Seille; Pauchet and Luquet, and Ylvisaker), the primary lesion was ulcerated in all, markedly obstructive in only one, perforated in two, annular in two and fungating in one, and there was dilatation of the proximal duodenal segment in three. Similar anatomic conditions were present in other cases in which vomiting was a marked symptom.

The vomitus or material removed for gastric analysis in twenty cases revealed the presence of bile in fourteen and blood in seven. The absence of bile from the vomitus in two cases can be attributed to the development of complete biliary obstruction. Free hydrochloric acid was absent in eight of fourteen specimens, and in one of these the reaction was alkaline. In the remaining six specimens the free hydrochloric acid varied from 5 to 100. The total acidity varied from 9 to 100 in nine specimens, being above 40 in 6. In Laning and Loy's case, in which the gastric contents were analyzed after the injection of histamine, the free hydrochloric acid and total acidity were unaffected in all specimens.

Jaundice.—Jaundice developed in three cases relatively late in the course. In Schofield's case the proximal margin of the growth encroached on the ampulla of Vater. In Meyer and Rosenberg's case 3 the primary tumor consisted of a large constricting mass just below the papilla of Vater, and there was marked dilatation of the biliary and pancreatic

ducts and suppurative cholangeitis. In our case 1 the proximal margin of the tumor was 2.5 cm. distal to the papilla of Vater and had extended proximally beneath the mucosa into the wall of the ampulla; the bile and the pancreatic ducts were further compressed by masses of tumor tissue in the duodenum, pancreas and retroperitoneal lymph nodes. The late development of jaundice is consistent with the observations made at autopsy in that obstruction to the extrahepatic biliary passages occurs relatively late from extension and metastasis to the pancreas, surrounding tissues and regional lymph nodes and exceptionally, in part, from the pressure of a large primary cancer. Of interest in this connection is the statement by Rivers and Thiessen that the appearance of icterus with obstructive lesions of the infrapapillary portion of the duodenum is an almost certain indication of malignancy.

Morbid conditions tending to cause biliary obstruction and jaundice were present in incipient form in several other cases. In Rolleston's case the tumor had reached the biliary papilla, and the common bile duct was dilated as a result of beginning obstruction. In Schiewe's case, although the papilla of Vater was encircled by neoplastic tissue, there was no apparent biliary obstruction and no jaundice. Similarly, in Dewis and Morse's case 7 and in our case 2 the common bile duct was slightly dilated, but jaundice was not yet apparent. Gallstones played no part in the production of jaundice, being present in only one instance and then in the gallbladder. Of the five cases in which there was partial or complete biliary obstruction, bile was detected in the gastric contents in two, was absent in one and was not mentioned in two.

Constipation and Diarrhea.—Constipation or obstipation was reported in nine cases, occasionally in association with roentgenographic evidence of stasis in the colon. Diarrhea occurred in five cases, as a transitory manifestation at the onset in two and in association with lead poisoning in another. So-called pancreatic diarrhea was reported only once. The stools of one patient were acholic, while those of two others, with bilious vomiting and tight strictures of the infrapapillary portion of the duodenum, contained bile. One patient with jaundice had stools which were dark because of the presence of blood.

Other Laboratory Data.—Patients with carcinoma of the infrapapillary portion of the duodenum tend to have marked anemia and slight leukocytosis, especially during the cachectic phase. Of nine cases in which it was possible to estimate the color index, it was high (from 0.9 to 1.1). An abrupt decrease in red blood cells was a terminal feature associated with loss of blood in the vomitus and stools. Evidences of impairment of hepatic and renal function were present in our case, with obstructive jaundice. Marked nitrogen retention occurred in one case, with incessant vomiting, nephrosis and an extreme degree of

duodenal obstruction. The results of urinalysis were reported in eighteen cases; in ten the urine was said to be normal; albumin was present in six, bile in three, indican in one and diminished amounts of chlorides and increased quantities of creatine in one.

Roentgenographic Studies.—Roentgenograms of the gastro-intestinal tract were taken after a barium meal in eighteen cases; in three the studies were unsatisfactory. In the others the findings were so varied that a brief analysis of each case seems warranted.

There were six cases in which the lesion was fairly well localized. In Pauchet and Luquet's case the barium did not pass beyond the fourth segment of the duodenum, the third portion being markedly dilated and having the appearance of the stomach. Anatomically, there was an ulcerated constricting lesion near the duodenojejunal junction. In Mateer and Hartman's case there were a filling defect in the third portion of the duodenum and stasis of barium in the proximal segments and stomach; at autopsy a large ulcerated lesion was found 4 cm. below the papilla of Vater. In Farinas Mayo's cases there were ptosis and distention of the stomach and dilatation of the duodenum up to its junction with the jejunum. Fluoroscopic examination showed active peristaltic and antiperistaltic movements, the barium being carried to the duodenojejunal angle; at the end of six hours almost the entire barium meal was still retained in the duodenum, which was maximally distended. Anatomically, there was a completely stenotic annular lesion at the duodenojejunal angle. In Lundberg's case the wide open pylorus was recognized, and the duodenum was well filled and very wide in its lower portion; strong peristalsis and successive contractions of the circular muscles were seen here, and the lumen was still filled after four hours. Autopsy disclosed a completely annular lesion at the duodenojejunal junction. In Sala's case there were dilatation and stasis of the duodenal cap and stasis and deformity of the descending portion of the duodenum, which was interpreted as being due to external pressure by a pancreatic tumor. Autopsy revealed an ulcer of the infrapapillary portion 5 cm. in diameter, extensive local adhesions and masses of cancerous lymph nodes; the pancreas, however, appeared to be normal. In Kellogg's case the gastric retention noted clinically was attributed roentgenographically to adhesions involving the second and the fourth duodenal segment; at autopsy an almost totally obstructive lesion was found near the terminal end of the duodenum.

There were five cases in which the roentgenographic picture suggested the presence of a lesion at or near the pylorus. In Deaver and Ravdin's case a roentgenographic diagnosis was made of adhesions or ulcer near the pylorus, the duodenum being reported as probably normal; at autopsy an ulcerated tumor was situated below the papilla of Vater.

In Vicker's case the column of barium was obstructed just beyond the pylorus, the stomach being huge and atonic; at laparotomy the tumor was found in the region of the duodenojejunal flexure. In Forni's case the duodenal bulb was partially filled with barium, but there was none in the remainder of the duodenum; at autopsy an annular almost totally obstructive lesion the size of a hen's egg was found in the third portion of the duodenum. In Harries and Harrison's case a filling defect of the pylorus was observed, with marked dilatation of the stomach, and a diagnosis of carcinoma of the pylorus was made; at laparotomy the neoplasm was found at the duodenojejunal flexure. In our second case a filling defect was observed at the pylorus, and at autopsy an annular stenosing cancer was found 11 cm. beyond the pyloric ring.

No suggestion of a lesion was observed roentgenographically in four cases, even though the morbid anatomic changes were striking. In Meyer and Rosenberg's case 3 there was marked obstruction by a fungoid mass, 5 by 6.5 cm., just below the papilla of Vater. In Davis' case there was a practically annular lesion, measuring 3.3 cm. in diameter, near the terminal end of the duodenum. In Laning and Loy's case the third portion of the duodenum was practically completely stenosed by an ulcerating mass 5 cm. long. The roentgenographic examination in Head's case was made seven months before death, and at autopsy the lumen of the intestine was almost completely occluded by a large cauliflower-like growth.

From an analysis of these data it is apparent that the accuracy of roentgenographic diagnosis in six cases is somewhat offset by the fact that in five the lesion was localized incorrectly at or near the pylorus and in four others no lesion could be demonstrated.

PHYSICAL EXAMINATION

A mass was palpated in the region of the primary tumor in five patients, and a doubtful or suggestive mass was felt in two. The mass was movable in three cases, moved with the respirations in one and was associated with tenderness in three and with rigidity in one. Tenderness was elicited in six other cases in which masses were not palpable, in two of which there was associated abdominal rigidity. In Schiewe's case marked pulsations were transmitted through a palpable tumor mass, which at autopsy was found to be adherent to a locally stenotic aorta. The presence or absence of a palpable mass was correlated with the size of the local tumor together with the associated inflammatory and neoplastic lesions; it was found that many large anatomic specimens were not detected during life, yet in one case an exceedingly small primary tumor was palpated. Conditions other than the primary tumor

were occasionally noted on palpation. For example, palpation of the liver and gallbladder gave evidence of biliary stasis, and metastatic lesions on the liver and in the deep and superficial lymph nodes were noted. Dilatation of the stomach, sometimes to the iliac crest, was noted in eight cases, often with visible peristalsis and a succusion splash, which Fenwick heard below the navel and laterally in the anterior axillary line.

DIAGNOSIS

The diagnosis of carcinoma of the stomach was made in ten cases, in six of which the growth was believed to involve the pyloric region. In twelve cases the following diagnoses were made: carcinoma of the small intestine, obstruction of the small intestine, pyloric obstruction, pyloric stenosis from ulcer, retroperitoneal tumor, carcinoma of the head of the pancreas, duodenal or jejunal stenosis, duodenal ulcer with carcinoma superimposed and organic obstruction at the duodenojejunal flexure.

A correct diagnosis was made at laparotomy in thirteen of twenty-one cases, and in three no diagnosis was recorded. The diagnoses made in five cases were: carcinoma of the small intestine, a mass of doubtful nature in the third portion of the duodenum, hypertrophy of the pyloric sphincter, retroperitoneal sarcoma and carcinoma of the pylorus. One patient was twice subjected to laparotomy, and a mistaken diagnosis of hypertrophied pylorus was made on each occasion.

TREATMENT

The treatment of carcinoma of the infrapapillary portion of the duodenum has been either symptomatic or palliative or directed toward cure. Rational therapy for definitely obstructive lesions has been outlined by Rivers and Thiessen with a view of combating the toxemia in preparation for operation. Radiation therapy was employed in two cases (Ylvisaker and Schofield). Laparotomy was performed in twenty-one cases, and the procedures and results are presented in the accompanying table. The results were unsatisfactory in seventeen cases, and the ultimate fate of the patients in the remaining four cases was not determined, two of them being alive three months after operation, one of whom had extensive metastases. Schofield's case is of particular interest in view of his original method of treatment. First he performed biopsy, cholecystoduodenostomy and posterior gastro-enterostomy and six weeks later reopened the duodenum and implanted radon seeds directly into the tumor. A duodenal fistula developed, and the patient died on the twenty-ninth postoperative day, but no evidence of neoplastic tissue could be detected at this time, the tumor evidently being quite radiosensitive.

A review of the morbid anatomic data in the present series of cases indicates the difficulties which may be encountered in carrying out surgical treatment. There was extension or metastasis or both in fifteen cases—in ten to regional lymph nodes, in five to the pancreas, in one

Results of Operation in Twenty-One Cases of Carcinoma of the Infrapapillary Portion of the Duodenum

Date	Authors	Operative Procedures	Period of Survival	Cause of Death
1904	Syme	Resection and end to end anastomosis	Alive 3 mo. later	
1917	Thaysen	Gastro-enterostomy	Died several days later	Hemorrhage
1919	Cade and Devic	Gastro-enterostomy	Died 36 hr. later	
1920	Deaver and Ravdin	Gastro-enterostomy	Died 2 hr. later	Shock
1924	Vickers	Gastro-enterostomy	Died 2 mo. later	
1924	Lundberg	Sept. ?: operation for traumatic rupture of intestine; Nov. 4: resection and end to end anastomosis	Alive 3 mo. later	
1925	Pommay and Seille	Gastro-enterostomy	Died 4 days later	Perforation and peritonitis
1927	Pauchet and Luquet	Resection		
1928	Dewis and Morse (case 7)	March 26: gastro-enterostomy; April 9: relief of obstruction due to kinking of bowel	Died 2 days later	
1929	Ylvisaker	Incision and drainage of pancreas	Died 15 days later	Hemorrhage
1930	Kellogg	Gastro-enterostomy	Died 8 days later	
1930	Schofield	April 16: cholecystoduodenostomy and gastro-enterostomy; May 28: radon seeds implanted	Died 29 days later	
1931	Meyer and Rosenberg (case 4)	Gastro-enterostomy and surgical ligation of duodenum	Died several weeks later	
1931	Forni	July 1930: exploratory; July 1931: gastro-enterostomy	Died about 3 mo. later	
1932	Mateer and Hartman	April: cholecystostomy; July: exploratory	Died 12 days later	Hemorrhage and shock
1934	Farinas Mayo	Resection		
1935	Davis	Resection and end to end anastomosis	Died 7 days later	
1935	Harries and Harrison	Resection and end to end anastomosis	Died 3 mo. later	
1935	Laning and Loy	March 15: cholecystostomy; March 25: gastro-enterostomy	Died 11 days later	Myocardial failure
1935	Sala	Exploratory	Died 5 days later	
1936	Author's case 2	Nov. 11: gastro-enterostomy; Nov. 17: incision of parotid abscess	Died 3 days later	Suppurative parotitis and pyemia

each to the posterior abdominal wall, surrounding fat and aorta and in approximately five to the ampulla of Vater and the common bile duct. Since these figures are based on routine autopsy, biopsy and surgical examination, it is probable that the true incidence of extension and

metastasis is much higher. Obviously all these factors must be taken into consideration in determining the therapeutic measures to be employed in individual cases.

SUMMARY AND CONCLUSIONS

A clinical and pathologic study is presented of thirty cases of carcinoma of the infrapapillary portion of the duodenum—two new cases and twenty-eight selected from the literature.

One of the new cases was found in 3,526 autopsies and the other in 20,176 autopsies.

Sixty-six per cent of the patients were men and 33 per cent were women; the average age was 58.2 years for the men and 48.3 years for the women.

The clinical onset was acute in 40 per cent of cases, with an average duration of four months; it was gradual throughout in 40 per cent, with an average duration of eleven months, and first gradual and then acute in 20 per cent, with an average duration of ten months, the gradual phase occupying four and a half months. The principal symptoms and signs irrespective of the mode of onset were pain, vomiting and cachexia. Other less common symptoms included anorexia, constipation, diarrhea, abdominal distention and jaundice. The vomitus or gastric contents were analyzed in twenty cases, and bile was detected in 70 per cent of these and blood in 35 per cent; free hydrochloric acid was absent in 57 per cent of fourteen specimens. A mass in the region of the primary tumor was palpated clinically in 16.6 per cent of the cases.

A correct preoperative clinical diagnosis is rarely made. An obstructing lesion of the duodenum was visualized roentgenographically with a fair degree of accuracy in 40 per cent of fifteen cases; in 33 per cent the lesion was incorrectly localized at or near the pylorus, and in the remainder no lesion was demonstrated. A correct diagnosis was made at laparotomy in 61.9 per cent of twenty-one cases, the results being unsatisfactory in 81 per cent of these, and the postoperative follow-up studies were incomplete in the remainder.

The primary tumor measured from 3 to 5 cm. in length in the majority of cases, and in one case the infrapapillary segment of the duodenum was involved diffusely in its entirety. All the tumors were of the glandular carcinomatous variety. The descending and ascending portions of the infrapapillary segment were most frequently involved. Extension of the primary tumor to adjacent structures and organs and metastases or both occurred in 50 per cent of cases. Some degree of obstruction of the terminal end of the common bile duct or of the ampulla of Vater or both occurred as a terminal feature in 16.6 per cent. Duodenal fistulas existed in 13.3 per cent. A high grade of

intestinal obstruction was present in 56.6 per cent. The alimentary canal proximal to the primary duodenal lesion was maximally distended, the stomach and proximal portion of the duodenum often giving the appearance of a bilocular viscus.

In dealing with duodenal cancer clinically or pathologically, the papilla of Vater is the most important anatomic landmark in this region.

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EXPERIMENTAL PEPTIC ULCER PRODUCED BY CINCHOPHEN

METHODS OF PRODUCTION, THE EFFECT OF A MECHANICAL IRRITANT AND THE LIFE HISTORY OF THE ULCER

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Cinchophen has been used since 1911 in the treatment of gout. Toxic cirrhosis of the liver has developed in a few cases after its use. In attempting to produce hepatic damage experimentally in dogs, Churchill and Van Wagoner [1] in 1931 noted peptic ulcer in many of their animals. This and subsequent work by these investigators suggested to us that we attempt to produce peptic ulcer by the administration of cinchophen. Ulceration developed readily in dogs after the administration of this drug. This led to a consideration experimentally of (1) the genesis and healing process of this type of ulcer, (2) the effect of a mechanical irritant and (3) the possibility of producing ulcer by the administration of cinchophen other than by the oral route.

REVIEW OF THE LITERATURE

Experimentally, the methods for the production of acute peptic ulcer have been many and relatively simple, while, on the other hand, the methods for the production of chronic peptic ulceration have been few and relatively difficult.

Churchill and Van Wagoner [1] (1931), in attempting to produce hepatic damage by the administration of cinchophen, noted from one to three gastric ulcers occurring in five of six dogs. The same authors [2] (1932) noted peptic ulcer in nineteen of twenty-four dogs which received cinchophen. The drug was mixed with the diet in amounts

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1. Churchill, T. P., and Van Wagoner, F. H.: Cinchophen Poisoning, Proc. Soc. Exper. Biol. & Med. **28**:581-582 (March) 1931.

2. Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning of Dogs, Arch. Path. **14**:860-869 (Dec.) 1932.

varying from the dose for man to twenty-seven times that amount. The earliest ulcers developed in eight and ten days. In 90 per cent of the animals the ulcers were situated in the gastric pathway and were generally multiple. Ulcer of the first portion of the duodenum developed in four animals. The major symptoms noted were anorexia, occasional nausea and vomiting, tarry stools and loss of weight.

Churchill and Manshardt [3] (1933) injected cinchophen in cottonseed oil into the jejunum daily and noted gastric ulcer in three dogs. They concluded that the ulceration was not attributable to a direct, local, toxic action of the drug on the gastric mucosa.

Shoji [4] (1933), using sixty rabbits and fifty dogs, gave doses of cinchophen varying from 0.1 to 0.2 Gm. per kilogram of body weight enterally and parenterally for from one to seven hundred days. Catarrhal inflammation and erosion were noted in the rabbits' stomachs, and ulcers formed in the dogs' stomachs.

Barbour and Fisk [5] (1933), who studied hepatic damage in dogs after the repeated oral administration of cinchophen, noted gastric ulcer in some of their animals.

Hanke [6] (1934), seeking an explanation for the origin of the ulceration that follows the administration of cinchophen, gave a series of cats large subcutaneous doses of a cinchophen preparation. Grossly the stomachs showed linear defects throughout the mucosa, and in many instances acute erosions and ulcerations were present. There were microscopic changes in the cells throughout the stomachs, but the greatest destruction was in the peptic cells.

Schwartz and Simonds [7] (1935) gave cinchophen in oil orally to cats, rabbits and guinea-pigs. Superficial erosions and ulcerations were

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3. Churchill, T. P., and Manshardt, D. O.: Experimental Production of Gastric and Duodenal Ulcers in Dogs in Cinchophen Poisoning, Proc. Soc. Exper. Biol. & Med. **30**:825-827 (April) 1933.

4. Shoji, Arata: Ueber den Einfluss von Atophan auf die inneren Organe von Kaninchen und Hund, mit besonderer Berücksichtigung der Magenschleimhaut, Tr. Soc. path. jap. **23**:520-522, 1933.

5. Barbour, H. G., and Fisk, M. E.: Liver Damage in Dogs and Rats After Repeated Oral Administration of Cinchophen, Ethyl Ester of Paramethyl-Phenylcinchoninic Acid (Tolysin) and Sodium Salicylate, J. Pharmacol. & Exper. Therap. **48**:341-357 (July) 1933.

6. Hanke, Hans: Experimental Production of Acute Ulcerative Gastritis by Parenteral Administration of Atophanyl, Internat. Clin. **1**:233-236 (March) 1935; Ueber experimentelle akute Atophanylgastritis als Erscheinungsform einer vorwiegend toxisch bedingten Gastritis, Beitr. z. path. Anat. u. z. allg. Path. **94**:313-331, 1934.

7. Schwartz, S. O., and Simonds, J. P.: Peptic Ulcers Produced by Feeding Cinchophen to Mammals Other than the Dog, Proc. Soc. Exper. Biol. & Med. **32**: 1133-1134 (April) 1935.

noted in the stomachs of the cats, but ulceration was not found in the stomachs of the rabbits or of the guinea-pigs.

Bollman and Mann [8] (1935) fed 1 Gm. of cinchophen to normal dogs five days a week. They noted peptic ulcer as early as the first week and as late as the fourteenth month.

No cases have been reported in which undisputed peptic ulcer due to cinchophen affected man. Reah [9] (1932) reported a case in which a patient died after therapy with cinchophen. Necropsy revealed a cirrhotic liver and a gastric ulcer. Bloch and Rosenberg [10] (1934) suggested the possible etiologic relationship of the cinchophen. They [11] reported a similar case in which necropsy revealed hepatic damage, multiple gastric ulcers and chronic gastritis.

METHOD OF INVESTIGATION

Seventy-seven dogs with an average range of weight varying from 8 to 17 Kg. were used in these studies. Each dog was normal before the experiments were begun. All normal dogs can be considered not to have peptic ulcer, as statistics have shown that it is rarely if ever present. The animals were given the routine kennel care, and the majority were fed a diet composed of cracker crumbs, ground horse meat and evaporated skimmed milk. The diet consisted of a calculated weighed amount known to be sufficient to meet the caloric requirement of the dog and will henceforth be called the "regular diet." A few dogs were given the regular kennel diet for contrast. This is a coarser meal consisting of dog biscuits and a cooked mash.

All surgical procedures were performed with the dogs under surgical narcosis induced by ether, and careful aseptic technic was employed. All dogs that were killed were given a light ether anesthesia and were then bled from the femoral arteries. These and the dogs that died were examined thoroughly. The handling and fixation of the specimens were considered extremely important. The stomach was carefully opened along the greater curvature on the anterior wall. At no time was any portion that was to be sectioned washed or wiped. The entire organ was stretched out and pinned to a piece of stiff cardboard; it was then fixed in a diluted solution of formaldehyde U. S. P. (1:10) for forty-eight hours or more. Multiple sections of all the organs were also fixed in a similar solution. All ulcers and multiple blocks of tissue removed from scattered regions throughout the stomach and duodenum were embedded in paraffin. These were sectioned semiserially and stained with hematoxylin and eosin.

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8. Bollman, J. L., and Mann, F. C.: Experimental Production of Gastric Ulcers, Proc. Staff Meet., Mayo Clin. **10**:580-582 (Sept. 11) 1935.

9. Reah, T. G.: Cinchophen Poisoning, Lancet **2**:504-509 (Sept. 3) 1932.

10. Bloch, Leon, and Rosenberg, D. H.: Gastric Ulcers Associated with Cinchophen Poisoning: Report of an Instance with Consideration of the Possible Etiologic Relationship, Am. J. Digest. Dis. & Nutrition **1**:29-31 (March) 1934.

11. Bloch, Leon, and Rosenberg, D. H.: Cinchophen Poisoning: Report of Seven Cases with Special Reference to Rare Instances Complicated by Multiple Gastric Ulcers, Am. J. Digest. Dis. & Nutrition **1**:433-437 (Sept.) 1934.

THE INCIDENCE OF PEPTIC ULCERS DUE TO CINCHOPHEN AND THE EFFECT OF A MECHANICAL IRRITANT

Physical agents which traumatize the gastric mucosa have been thought to be an etiologic factor in peptic ulcer. Fauley and Ivy [12] (1930) found that coarse particles remain in the stomach longer than do fine particles. Obviously, the coarse particles produce prolonged motor activity of the stomach and an increase of trauma to an acute lesion of the mucosa. These investigators have produced chronic lesions from acute ulcers and have prolonged the healing time of acute lesions by feeding mechanical irritants.

Walker [13] (1931) removed a portion of gastric mucosa from the stomach of several rabbits. A persistent mechanical irritant formed by a suture line directly beneath the lesion delayed the healing and increased the development of chronic ulceration.

Mann and others have demonstrated the presence of a mechanical factor in the production of peptic ulcer.

Our experiments on this phase of the subject follow:

Methods.—Fifty-one dogs were used in this study. These were divided into three groups. Group 1 consisted of twenty-eight dogs with an average weight of approximately 16 Kg. Twelve of them were fed the regular diet, and sixteen were fed this diet plus 100 Gm. of coarsely ground bone. The bone was given to determine the effect of mechanical irritation on the production and healing of the peptic ulcer. Regardless of the dog's size or weight, 2 Gm. of cinchophen well mixed with the diet was given daily to all animals. This is approximately three times the maximal daily dose for man and a fifth of the minimal lethal dose for dogs.

Clinically, the diagnosis of ulcer depended on the following symptoms: (1) vomiting of small amounts of gastric contents, (2) a tarry diarrhea of variable, but increasing severity, (3) anorexia, (4) anemia and (5) loss of weight and activity. If death did not occur at this stage from perforation of the ulcer, an exploratory operation was usually done and the presence of an ulcer confirmed.

Group 2 consisted of twenty dogs with an average weight of approximately 9 Kg. All were fed the kennel diet and were given 1 Gm. of cinchophen mixed with the meal daily five days a week. No drug was given the last two days of each week. It was intended in this way to determine the effect of the prolonged administration of a small dose of cinchophen. In every case the drug was given until the dog died or was killed.

Group 3 consisted of thirteen dogs. These were used as controls and did not receive any cinchophen. Three were fed the regular diet plus bone, and ten were fed the kennel diet. They were killed and examined after a longer period of observation than were any of the animals which received cinchophen.

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12. Fauley, G. B., and Ivy, A. C.: Experimental Gastric Ulcer: The Effect of the Consistency of the Diet on Healing, Arch. Int. Med. **46**:524-532 (Sept.) 1930.

13. Walker, M. A.: Healing of Gastric Mucous Membrane in Rabbits After Its Surgical Removal, Arch. Path. **12**:85-89 (July) 1931.

Results.—Group 1.—Peptic ulcer developed in twenty-seven (96.4 per cent) of this group of twenty-eight animals. No animal was given cinchophen longer than sixty consecutive days. The one dog which did not have an ulcer did not reveal any noticeable effect of the drug.

Of the twenty-seven dogs which had an ulcer, nine (32.1 per cent) had multiple ulcers, and eighteen (64.3 per cent) had a single ulcer. All were gastric ulcers. Two (7.1 per cent) of the dogs had an associated duodenal ulcer. Twenty-five (89.3 per cent) had a pyloric ulcer situated from 2 to 3 cm. from the pyloric ring on the posterior wall and lesser curvature of the stomach (fig. 6). No ulcer was seen on the greater curvature. Frequently small contact ulcers were found about a large chronic ulcer. The multiple ulcerations were spread over the entire gastric mucosa but were most marked in the pyloric and fundic regions.

In the sixteen dogs that were fed bone, ulcer developed clinically in an average of seven days after the administration of 14 Gm. of cinchophen. Ulcer developed in eleven of the twelve dogs that were not fed bone in an average of eighteen days after the administration of 36 Gm. of cinchophen. The incidence of perforation was slightly higher, although not significantly so, among the animals which were fed bone. There were seven (43.7 per cent) perforations among the latter animals, as compared with four (33 per cent) among the animals that did not receive bone.

The condition of all animals at the time of necropsy was good; little alteration was observed in the nutritional state. In many instances the dog gained weight. Where there was a loss of weight, it was relatively insignificant, usually being from 0.5 to 1.2 Kg.

Roentgenographic studies were attempted for diagnostic purposes, but the difficulties encountered did not warrant the continuance of such studies. Roentgenoscopic examination of five dogs in this group revealed the presence of an ulcer in four of them. Exploratory operation revealed the presence of an ulcer in all of the five dogs.

Group 2.—Peptic ulcer developed in nineteen of the twenty dogs in this group (animals given 1 Gm. of cinchophen five days a week). The dog which did not have an ulcer received 281 Gm. of cinchophen in four hundred and eighteen days. This dog gained 5 Kg. and showed no noticeable effect of the drug. The animals in this group received an average total dose of 198 Gm. of cinchophen in two hundred and seventy days. The smallest dose was 22 Gm. in thirty days and the largest was 423 Gm. in six hundred and thirty days. Four of the dogs gained weight, but there was an average loss of 0.35 Kg.

Seven (35 per cent) of the nineteen dogs had multiple ulcers, and twelve animals (60 per cent) had a single ulcer. In every case there was a gastric lesion, although two dogs (10 per cent) had an associated duodenal ulcer. In seventeen instances (85 per cent) a chronic ulcer was situated in the pyloric region, on the posterior wall and the lesser curvature of the stomach. One animal (5 per cent) had an ulcer on the anterior wall of the stomach near the lesser curvature. No ulceration was observed on the greater curvature. Perforation occurred in two (10 per cent) of the dogs.

The time of development of the ulcers was variable. In two dogs exploration was done six months after administration was commenced, but no lesion was noted; six months later an ulcer was found in each animal. An ulcer was found in other animals on the twenty-second, sixty-first and one-hundredth day after administration of the drug, but one animal did not have symptoms until the six hundredth day.

GROUP 3.—The thirteen control dogs which did not receive the drug were normal in every respect. There was no macroscopic or microscopic lesion of the gastric mucosa of the three dogs which received bone in their diet.

Comment.—These studies demonstrate that the oral administration of cinchophen will produce peptic ulcer in nearly 100 per cent of all dogs. It seems logical that the presence of any mechanical irritant, such as bone, might cause microscopic damage to the mucosa, thus making it susceptible to early damage by cinchophen; or that the drug might cause the original injury and the trauma produced by the bone might aid in the development of the ulcer and production of early symptoms. The latter is more probable, because in no case were we able to demonstrate microscopic damage of the mucosa when cinchophen was not given.

No reason can be given for the failure of peptic ulcer to develop in two of the dogs.

That the general nutritional condition of the dogs was not responsible for the development of ulcer is significantly shown by the following findings: 1. Ulcer occurred in many dogs before any alteration in the nutritional state could be observed. 2. Many of the dogs gained weight; when there was a loss of weight, it was relatively insignificant.

It is interesting to note that perforated ulcer was less frequent in the animals which received doses of 1 Gm. of cinchophen than in animals which received larger amounts of the drug. This suggests that the smaller doses of the drug do not inhibit the healing processes as much as do the larger amounts.

A comparison of the situation of ulceration in man with that in animals is of interest. From 10 to 40 per cent of the peptic ulcers which affect man are multiple. From 70 to 95 per cent of the gastric ulcers which affect man are situated along the *Magenstrasse* in the pyloric region. These facts were found true of the ulcers which developed in the dogs. However, the number of gastric ulcers after the administration of cinchophen as compared to the number of duodenal ulcers is in exact reversal of the situation of peptic ulcer as seen in man. This is possibly attributable to the fact that the gastric mucosa of animals appears to be more affected by toxins than does the duodenal mucosa. The duodenal ulcers in the animals were in a situation comparable to that of the usual duodenal ulcer in man. Ulceration of the greater curvature is rarely seen in human beings, and it was not observed in the dogs.

THE EFFECT OF CINCHOPHEN WHEN ADMINISTERED OTHER WAYS THAN ORALLY

We have mentioned that peptic ulcer has been produced by the administration of cinchophen directly into the jejunum and parenterally. We administered cinchophen rectally, intravenously and subcutaneously

and by injection into an intestinal fistula to determine whether or not an ulcer would develop in the same manner as it did when the drug was given orally.

Injection into Intestinal Fistula.—Four dogs with an average weight of 15 Kg. and low jejunal or high ileal fistulas were used. Approximately 2 Gm. of cinchophen suspended in cottonseed oil was instilled daily through a catheter directly into the jejunum or ileum. Gastric ulcer, and in one instance, an associated duodenal ulcer, occurred in all four animals. The average time required for development of the ulcer was twelve days. There was no injury at the site of the injection of the drug.

Rectal Administration.—Two dogs weighing 19 Kg. were given a daily colonic irrigation; 4 Gm. of cinchophen in cottonseed oil then was instilled into the rectum. The animals showed symptoms referable to the action of the drug and were killed at the end of five days after the administration of the drug. Multiple acute gastric ulcers were found in both dogs. There was no injury to the rectum.

Parenteral Administration.—A neutral solution of the sodium salt of cinchophen was prepared for intravenous use. Each of two dogs, which weighed 18 Kg., was given an initial dose of 0.1 Gm. This was increased daily until a maximal dose of 2 Gm. had been reached. Definite symptoms were noted when a dose of 0.5 Gm. was given. These symptoms became progressively more severe as the dose of the drug was increased.

Immediately after the injection of 2 Gm. of the drug there were an increase in the nasal secretions, an increase in both the depth and the rate of respiration and an associated slowing of the beat of the heart. These symptoms were occasionally accompanied by involuntary micturition, forceful defecation and nausea and vomiting and rarely by a clonic twitching of the muscles. Fifteen minutes after the drug was given the symptoms disappeared, but the dogs remained stuporous for three hours. The most severe symptoms always occurred during the first hour. After the three hour period the animals appeared well and would eat as usual.

A more prolonged and a more gradual effect was desired; therefore, a daily subcutaneous injection of 2 Gm. of cinchophen suspended in cottonseed oil was substituted for intravenous administration. When the drug was thus administered, some symptoms were present by the end of the first hour. These reached their peak within three hours and gradually subsided during the next twelve hours.

Symptoms of ulcer developed in both dogs in one week. One dog was killed, and multiple acute gastric ulcers were present. The administration of cinchophen to the second dog was continued for an additional week. The dog was then killed. Two large subacute ulcers were found in the pyloric region on the lesser curvature and posterior wall of the stomach. There was an associated diffuse gastritis.

Two other dogs were given cinchophen intravenously for a period of less than one week. These were killed after one or two tarry stools had been passed. Microscopic lesions were found in the stomach of each dog.

THE DEVELOPMENT OF ULCER IN FUNDIC POUCHES

Method.—Fundic pouches were made in five dogs with an average weight of 11.5 Kg. This was done by cutting away a portion of the greater curvature of the stomach, forming it into a pouch and allowing it to drain through a de Pezzer catheter into a balloon which was carried at the side of the dog. These pouches were made primarily for a study of the gastric secretion, but in this paper mention will be made only of the results in regard to formation of ulcer.

Daily doses of cinchophen, which varied from 0.25 to 2 Gm., were mixed with the diet. The dogs were killed when they showed marked symptoms from administration of the drug or when the studies of the gastric secretion had been terminated.

Results.—Within four hours after 2 Gm. of cinchophen had been given orally, a small amount of macroscopic blood was present in the secretion in the pouch. The bleeding increased until the seventh hour. At this time the content of the pouch was cherry red. From the eighth to the twelfth hour after the oral administration of the drug, there was a rapid decrease in the amount of bleeding. Between the twelfth and the twenty-fourth hour, the secretion in the pouch was again clear. This same sequence occurred after each daily dose of cinchophen. The bleeding became progressively more severe, until at the time of definite formation of an ulcer there was some bleeding most of the time, but from the fourth to the twelfth hour after administration of the drug there was actually a hemorrhage. The amount of bleeding varied directly with the amount of drug given. The smallest dose of cinchophen that would produce an ulcer (0.5 Gm.) was the smallest dose that caused bleeding.

Ulceration developed in the pouches of all five dogs (fig. 1). Usually multiple, acute to subacute perforating lesions were found. In three animals the ulcer perforated the wall of the pouch. The other two had a microscopically perforating ulcer but were killed too early for gross perforation to occur. Ulcer formed in the pouch in from two to five days when the dose of cinchophen was 1 Gm. or more daily.

The stomachs in all five dogs were relatively free from injury, although superficial ulceration was noted at the lower end of the healed suture line (fig. 1) in four of the five dogs. There were also a few scattered linear erosions and mild gastritis. In no instance, however, was there a definite chronic ulcer in the stomach.

To determine whether or not cinchophen was being secreted into the isolated gastric pouches, several quarts of the secretion obtained from the pouches of dogs which were receiving cinchophen by mouth was concentrated by prolonged evaporation. This mixture was then subjected to a colorimetric test sensitive for cinchophen in amounts of from 0.01 to 0.1 Gm. A positive reaction was not obtained.

One quart of a mixture of the content of the pouch, which was not evaporated, was mixed with the diet of a dog which weighed 11 Kg. This was done daily for two weeks, and the stomach was then examined at necropsy. Ulceration was not found.

Comment.—These studies demonstrate that the administration of cinchophen by routes other than the mouth is equally effective in the production of peptic ulcer. They conclusively prove that the action of the drug is not local but occurs after absorption.

The rapidity with which symptoms appeared and then disappeared after the intravenous administration of the drug and the rapidity with which bleeding occurred in the fundic pouch and then as quickly subsided suggest that cinchophen is rapidly absorbed and rapidly excreted or destroyed. It is probable that the toxic effects and the excretion of the drug were nearly complete twelve hours after administration and were entirely complete after twenty-four hours.

The fact that acute ulcer occurred rapidly and was always of the perforating type in the fundic pouch lends support to the acid factor as

an important element in the production of the ulcer. The drainage of the pouch was never complete; no alkalinizing mechanism was present, and at most times there was some free acid in the contents. The stomach of each dog showed little injury. It seems likely that once the original mucosal destruction had occurred, the constant presence of the free acid in the pouch increased the rate of formation of ulcer.

The negative results obtained with the colorimetric test and the failure to produce ulcer by feeding the contents of the pouch to a dog suggest that cinchophen as such is not secreted by the gastric mucosa. It is possible that it may have been present in an amount too small to

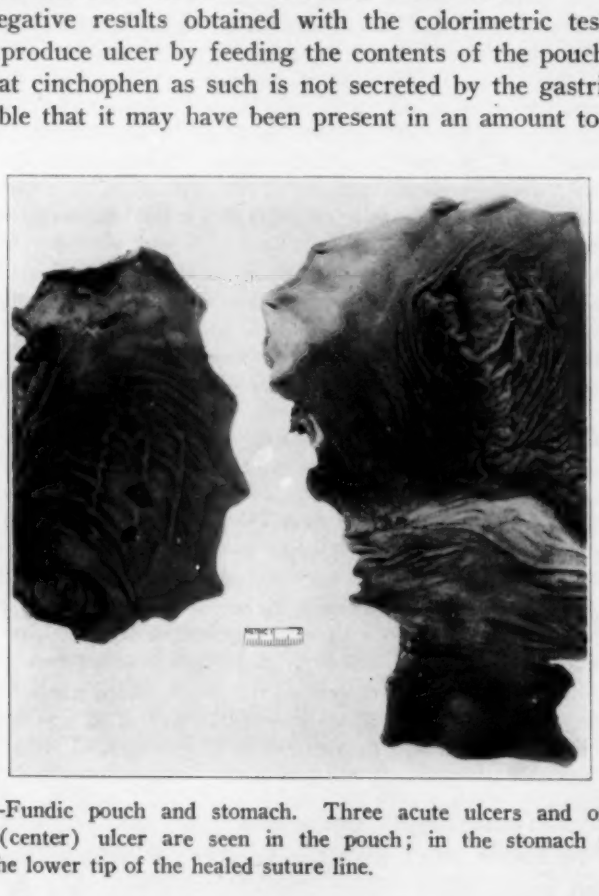

Fig. 1.—Fundic pouch and stomach. Three acute ulcers and one subacute perforated (center) ulcer are seen in the pouch; in the stomach there is an erosion of the lower tip of the healed suture line.

detect with the method at hand or that it was present in a chemically changed form.

THE PATHOLOGIC STRUCTURE OF THE PEPTIC ULCER PRODUCED BY CINCHOPHEN

Van Wagoner and Churchill (1932) described the early ulcer due to cinchophen. They noted a destruction of the mucosa in the depth of a crypt. The mucosal cells were necrotic and covered with a layer of fibrin and polymorphic leukocytes. Radiating from the ulcer into the underlying tissue was an acute inflammatory reaction.

It is most frequently stated that peptic ulcer in man begins as a series of diffusely scattered acute ulcers. These tend to heal, and those in which the reparative process is less than the destructive process become chronic.

Mann [14] (1925) observed the healing process in experimental peptic ulcers. He noted that there is first a clearing of the base of the ulcer and then the formation of a granulation tissue bud, which tends to fill the crater. At the same time there is a subsidence of the inflammatory reaction and a proliferation of the connective tissue. The mucosa then grows in from the edge and covers the granulation tissue as a single layer of epithelium. This layer rapidly becomes polypoid, and finally there is an atypical epithelium on a base of scar tissue.

Caylor [15] (1926 and 1927) and Bliss [16] (1932) reported a similar process in the healing of peptic ulcer in man.

Our experiments on this phase of the subject follow:

Methods.—Three dogs with an average weight of 17 Kg. were given 2 Gm. of cinchophen daily in a regular diet. Regardless of the presence or absence of symptoms, they were killed at intervals of five days. Multiple sections were taken from various regions of the stomach and duodenum. These were stained and studied microscopically for the presence of the early lesion.

In addition to these three dogs, all of the animals previously mentioned were used in this study. The diets and the doses of cinchophen which were administered have already been described. Each lesion was studied grossly and microscopically. To obtain the healing ulcer, exploratory laparotomy was performed; the presence of an ulcer was definitely confirmed, and its size and situation was determined. The administration of cinchophen was stopped on the day of the exploration. Postoperatively the dog was fed his previous diet without the drug. The animals were killed at definite periods, which varied from three days to twelve weeks after administration of the drug had been commenced. The specimens were treated and sectioned as described previously.

Results.—All of the specimens obtained from the animals used in this study were examined macroscopically and microscopically. These animals had received cinchophen in variable doses for variable periods of time. This afforded an opportunity for the study of the various stages in the development and the healing of ulcer. We have summarized these results and present them as a composite general picture.

The Early Lesion: Each dog that had had one or more tarry stools had a lesion of the gastric mucosa. A diffuse gastritis was usually present after the third or fourth dose of 2 Gm. of cinchophen (fig. 2). The entire stomach was

14. Mann, F. C.: Production and Healing of Peptic Ulcer, Minnesota Med. **8**:638-640 (Oct.) 1925.

15. Caylor, H. D.: The Healing of Gastric Ulcer in Man, Ann. Surg. **83**:350-356 (March) 1926; The Healing Process of Gastric Ulcer in Man, ibid. **86**:905-917 (Dec.) 1927.

16. Bliss, T. L.: Healing of Chronic Duodenal Ulcers, Am. J. Surg. **15**:93-98 (Jan.) 1932.

somewhat edematous and hemorrhagic in appearance. The mucosa was covered with an excess of mucus. Beneath this mucus and scattered over the entire mucosa, but chiefly throughout the fundic and pyloric regions, was an adherent layer of black altered blood. This appeared as a covering or as isolated pinpoint clots. Many of the clots were covered by folds of mucosa.

Multiple fine linear erosions were seen scattered between these blood clots. If a blood clot was removed, it was found that it filled one of these erosions. Occasionally there were superficial clean-appearing punched-out mucosal ulcerations. These usually were situated along the lesser curvature and varied from 1 mm. to 1 cm. in diameter.

Microscopically, sections through the area of gastritis demonstrated regions in which there were several necrotic mucosal cells sloughing into the lumen of the

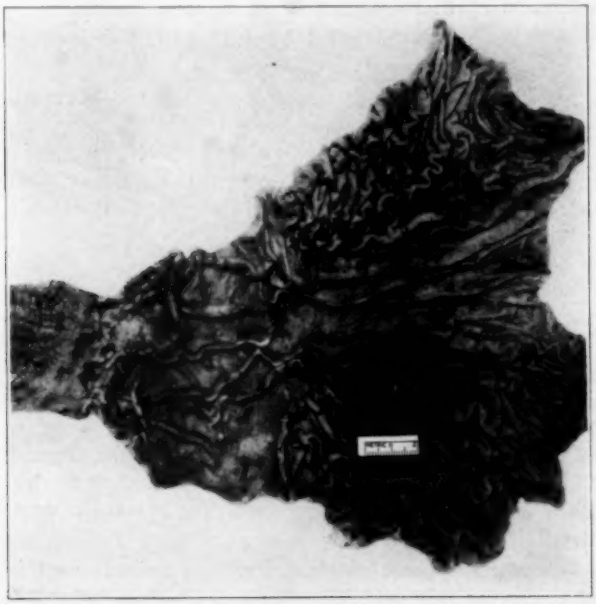

Fig. 2.—A specimen showing diffuse gastritis. An edematous mucosa, with multiple adherent blood clots, a few linear erosions and small ulcerations are seen.

stomach (fig. 3). These were surrounded by a superficial inflammatory reaction, which consisted chiefly of polymorphonuclear leukocytes and involved only the mucosa. In many instances a bleeding mucosal blood vessel was noted. Throughout the stomach there were edema of the mucosa, a congestion of the mucosal blood vessels and an increase in the cellular elements, particularly of the round cells.

In the majority of instances the erosions rapidly developed into acute peptic ulcers. If a dog was killed during this acute ulcerative stage, from thirty to sixty acute gastric ulcers were found (fig. 4). These ulcers had a fresh and punched-out appearance. The edges were cleancut, smooth and not edematous. The floor of each ulcer was usually smooth, firm and clean but at times was covered by a thin layer of blood. No granulation or pus was seen on the surface of an ulcer. The size of the ulcers varied from 2 mm. to 1 cm. in diameter. The acute ulcers

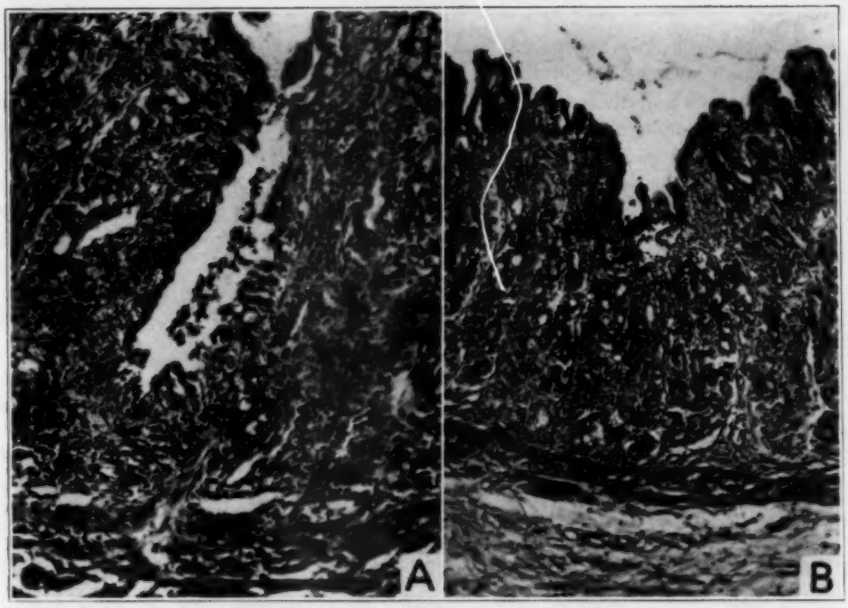

Fig. 3.—*A*, a photomicrograph of the earliest microscopic lesion, showing necrotic mucosal cells sloughing into the lumen of a crypt; × 120. *B*, a photomicrograph of a slightly more advanced lesion than is shown in *A*, picturing destruction of the mucosal cells with a surrounding inflammatory reaction; × 85.

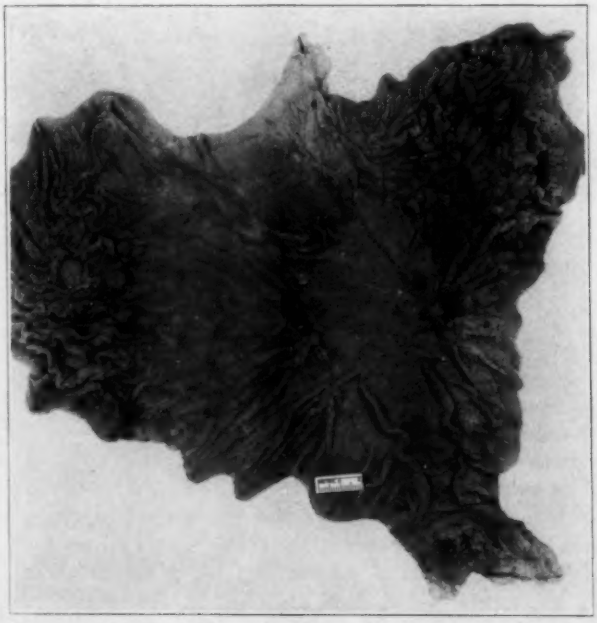

Fig. 4.—A specimen showing multiple acute to subacute gastric ulcers.

usually involved only the mucosa and submucosa but at times involved all layers of the stomach and even perforated.

Microscopically, there was a sharply defined ulceration with a zone of neutrophilic infiltration in the floor of an ulcer (fig. 5). This frequently extended for a considerable distance below the necrotic layer, but for the most part the surrounding tissue had a healthy appearance. There was some edema, especially of the submucosa. The vessels were congested but showed no endothelial thickening. The muscle layer was frequently infiltrated with polymorphonuclear neutrophils.

The Late Ulcer: The multiple acute ulcers healed rapidly, and the diffuse gastritis disappeared. There persisted in the "ulcer-bearing" area a large chronic ulcer situated from 2 to 3 cm. from the pyloric ring on the lesser curvature and posterior wall of the stomach (fig. 6). Occasionally several acute to subacute

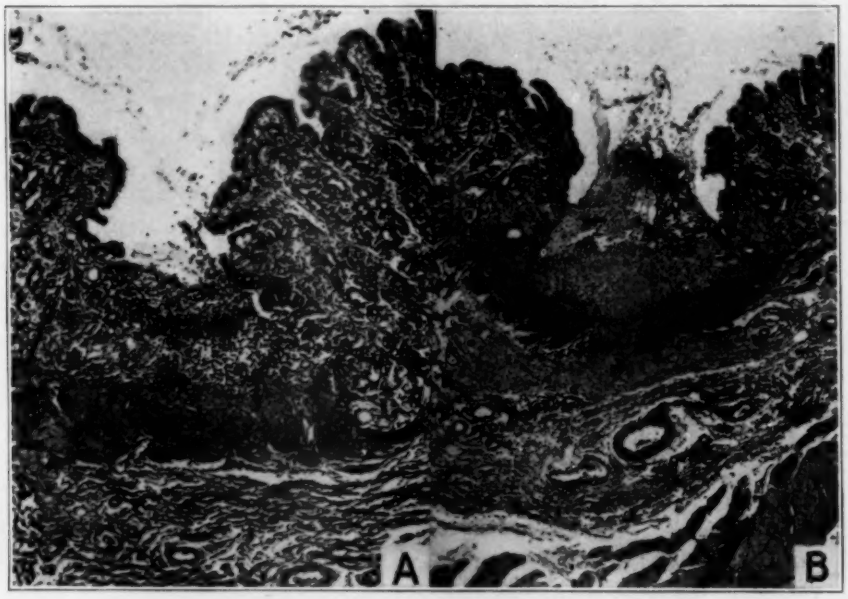

Fig. 5.—*A*, photomicrograph of an acute gastric ulcer with beginning involvement of the muscularis mucosa; × 60; *B*, a photomicrograph of an acute gastric ulcer with involvement of the muscularis mucosa and beginning infiltration of the submucosa; × 30.

ulcers were associated with this chronic ulcer, but there was never more than one chronic ulcer in a single specimen.

The chronic ulcer had an old appearance; it was thick, indurated and rounded and had overhanging edges. There was a dirty, necrotic or granulating floor. At times this floor was formed by the adjacent tissue, namely, the pancreas or liver. Occasionally there was a visible perforation through the base of the ulcer. This was associated with either a localized abscess or a general peritonitis.

Microscopically, there was a superficial zone of molecular necrosis (fig. 7) which rested on vascular granulation tissue. This granulation tissue was markedly infiltrated with fibrous connective tissue and lymphocytes. The muscle layer

Fig. 6.—A specimen showing a chronic perforated gastric ulcer on the lesser curvature of the stomach with multiple contact ulcers. Thirty-four grams of cinchophen was given in nineteen days.

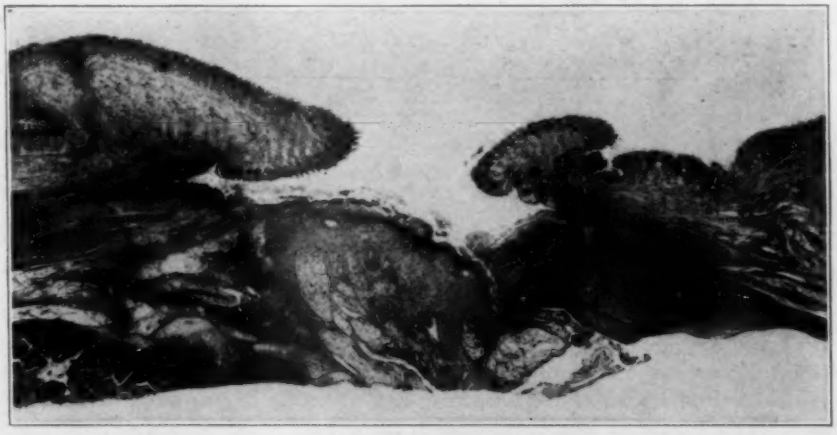

Fig. 7.—A photomicrograph of a chronic perforated ulcer of the lesser curvature of the stomach showing the undermined and rolled over edges, a superficial necrotic layer on a fibrous granulation tissue base and involvement of the omental fat and pancreas in the base; × 37½.

was always penetrated and infiltrated with lymphocytes. In many cases the muscle had been replaced by the infiltrated pancreas or fibrous pads of gastrohepatic omentum.

The entire process extended for a short distance laterally. The blood vessels showed endarteritic and endophlebitic thickening with a large number of newly formed vessels. The general shape of the ulcer was variable but was usually funnel shaped or cone shaped.

At the margins of the ulcer there was evidence of proliferative activity on the part of the mucosal epithelium. The slough was lifted a bit or partially removed, and new mucosal cells were seen forming on a clean granulation tissue.

Healing Process: There was a constant attempt at healing in the peptic ulcer produced by cinchophen. When the administration of cinchophen was discontinued,

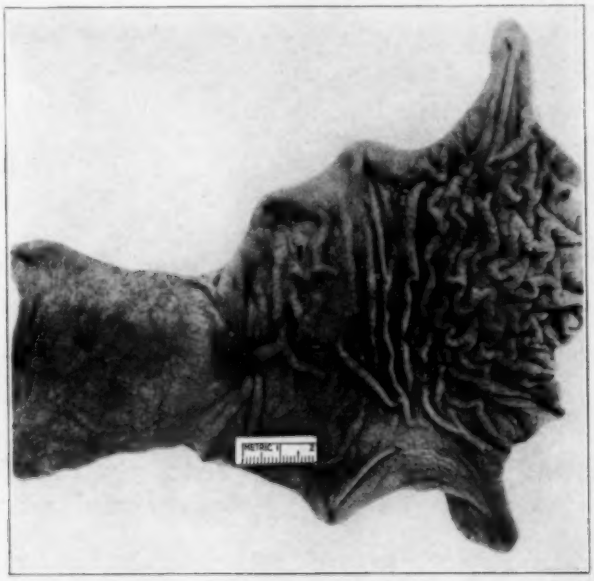

Fig. 8.—A specimen showing a chronic perforated ulcer of the lesser curvature of the stomach after two weeks' healing. The crater is nearly filled with clean granulation tissue; a fibrinous blood clot is seen in the center.

healing of the ulcer rapidly took place. This process was so rapid that no significant difference could be noted when the regular, the kennel or the bone diet was given. The time required for complete healing of the chronic ulcer was from three to five weeks. Complete healing was noted as early as two weeks, but some ulcers required more than seven weeks to heal. Occasionally the ulcer healed while the animal was receiving cinchophen. This was noted only in the dogs which received 1 Gm. of the drug five days a week. It was never noted in the dogs which received 2 Gm. of cinchophen daily.

Three days after the administration of cinchophen was discontinued the ulcer had a much cleaner appearance than before. The superficial necrotic layer had disappeared. The clean base was covered by a thin fibrinous blood clot. This clot disappeared at the end of one week after administration of the drug was

discontinued. The crater was being filled with vascular, friable, granulating tissue (fig. 8). By the tenth or twelfth day the granulation tissue had a polyp-like appearance and more than filled the crater. The mucosa could be seen growing over the granulation tissue from the edges of the ulcer.

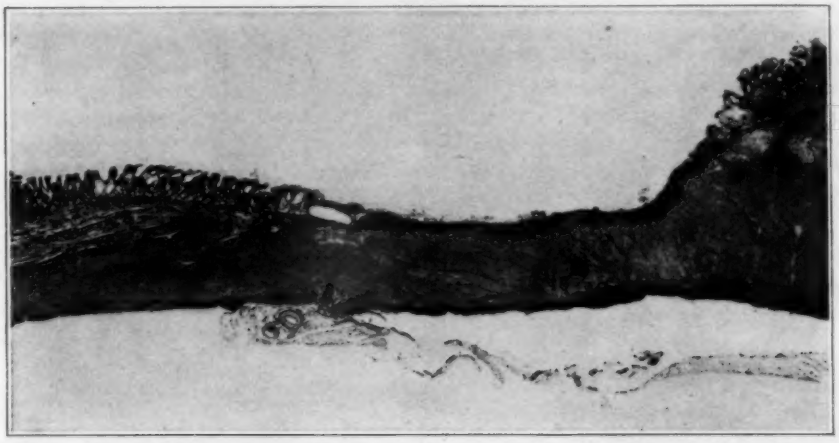

Fig. 9.—A photomicrograph of a chronic gastric ulcer after healing for one week; × 6. One may note the clean granulation layer with the marginal epithelization.

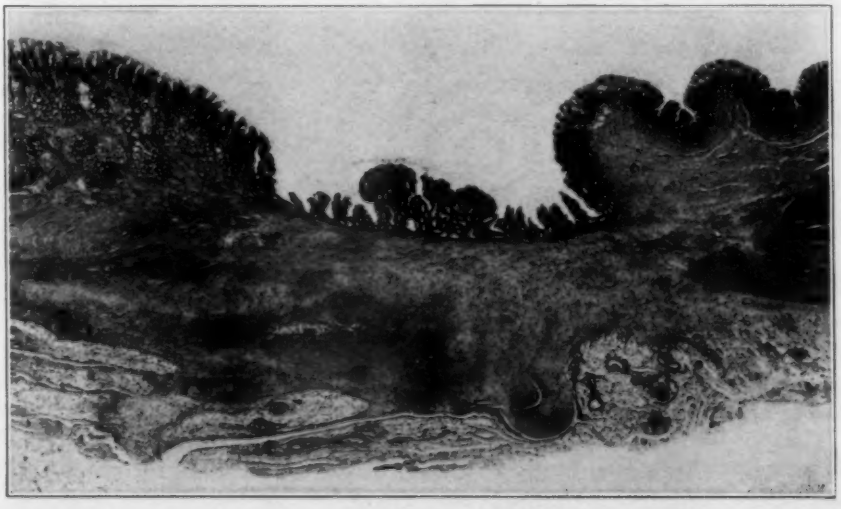

Fig. 10.—A photomicrograph of a chronic gastric ulcer during healing with newly formed mucosa becoming polypoid on a vascular scar tissue base; × 4½.

Microscopic examination revealed the same changes as were seen grossly (fig. 9). In addition, a subsidence of the inflammatory reaction and marked proliferation of the fibrous tissue in the base of the ulcer were noted. The marginal

epithelium was seen growing as a single layer of flat or cuboidal cells over the granulating tissue. As this layer of cells progressed, the polyp-like projection of granulation tissue was pinched off. The new mucosal cells rapidly became columnar and were thrown into folds, which in turn formed villi (fig. 10). The mucosal glands then regenerated.

The damaged muscular layer was replaced by fibrosis. This fibrosis extended laterally beyond the defect and in some cases involved the serosa. Many of the blood vessels were obliterated, but many new ones were formed. The completely healed ulcer (fig. 11) was a scar-filled excavation covered by atypical epithelium.

Grossly, this completely healed ulcer (figs. 12 and 13) was recognized early by the raylike arrangement of the surrounding rugae. The regenerated epithelium had a whiter, more roughened and depressed surface than the surrounding mucosa.

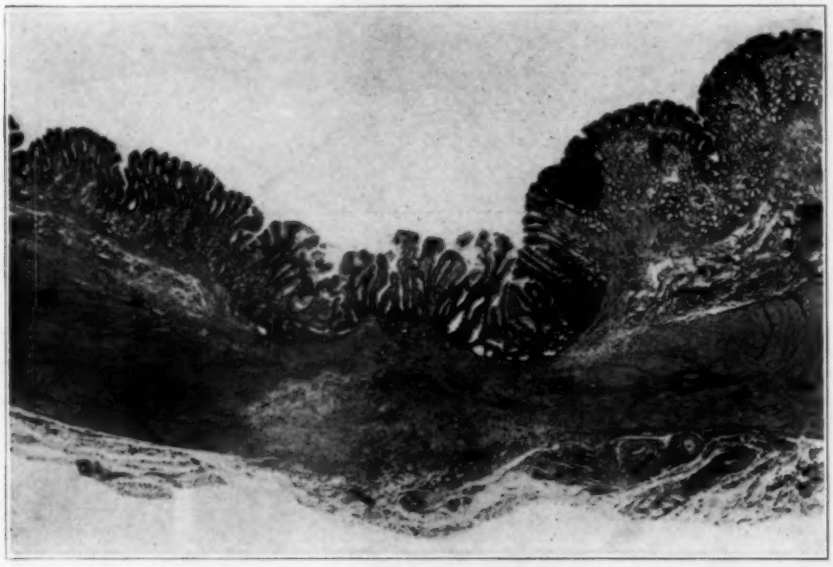

Fig. 11.—A photomicrograph of a completely healed chronic gastric ulcer, showing atypical mucosa on a scar tissue base; × 10.

The healed ulcer was recognized with much greater difficulty at the end of twelve weeks. The mucosa appeared nearly normal, but there remained a persistence of the raylike rugae. Occasionally, the ulcer was recognized by the thickened white fibrous appearance of the serosal surface.

The majority of the dogs which were fed bone had particles of this bone embedded in the fibrotic layer of the healed ulcer. Several active ulcers contained hair, bone and other foreign bodies embedded in the base.

The gross and microscopic pictures of the duodenal ulcer are identical with those of the gastric ulcer.

Comment.—These studies demonstrate that the peptic ulcer produced by cinchophen begins with a destruction of mucosal cells. This occurs throughout the gastric mucosa and is associated with diffuse gastritis. There is hemorrhage from the mucosal blood vessels. The mucosal

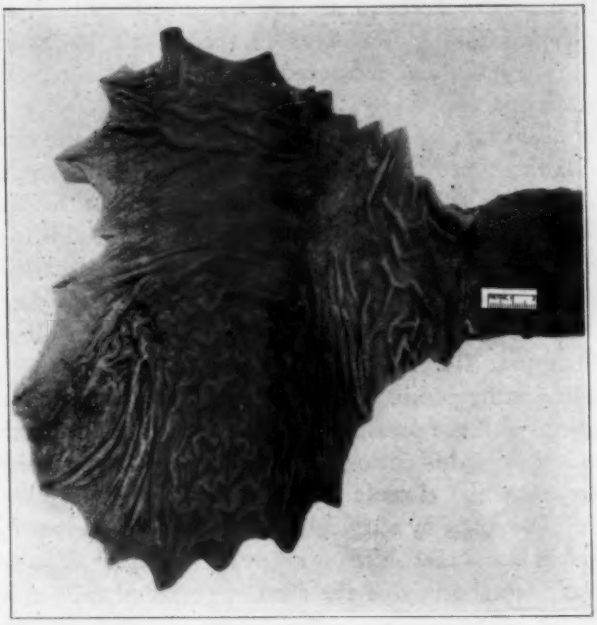

Fig. 12.—A specimen with a chronic perforated ulcer on the posterior wall after six weeks' healing, showing the mucosa rolled from above over a small unhealed crater and spokelike contraction of the mucosal folds.

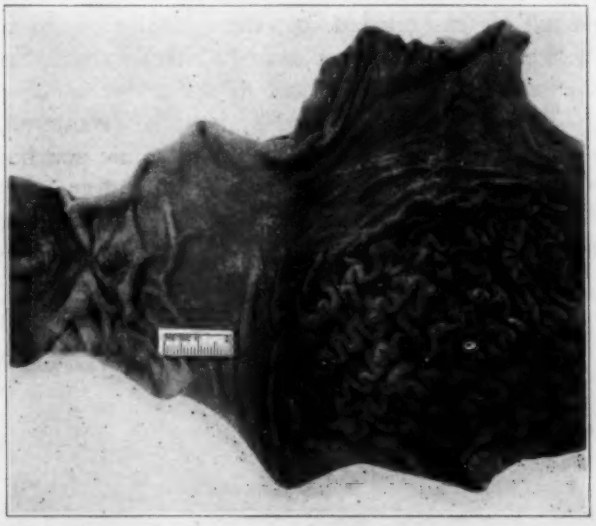

Fig. 13.—A specimen with a completely healed chronic perforated pyloric ulcer of the lesser curvature.

erosions progress as a result of digestion by the gastric contents and become multiple acute ulcerations. These acute ulcers heal, and the gastritis disappears. The acute ulcers in the gastric pathway, probably because of the trauma and increased digestion of tissue, progress and become chronic ulcers.

An ulcer heals rapidly when the administration of the cinchophen is stopped. The fact that the feeding of bone made no apparent difference in the rate of healing is interesting. It was shown that this traumatizing agent contacted the ulcer, because it was found embedded in the base of the ulcer. It cannot be definitely said that this irritant had no effect on the rate of healing, but there was none that could be accurately demonstrated. The etiologic factor was removed when the administration of the drug was stopped.

Pathologically, the peptic ulcer produced by cinchophen was identical in every respect with the peptic ulcer seen in man. The final true ulcer is a chronic lesion. This then gives us a method for consistently producing an experimental chronic peptic ulcer. This could be done consistently heretofore only by surgical means. This process presents itself as an invaluable one, because it opens up to a greater degree the possibility of experimental study of the chronic peptic ulcer.

SUMMARY

The administration of cinchophen is an effective method for the production of chronic peptic ulcer in dogs. Peptic ulcer developed in 95.8 per cent of the animals after the oral administration of cinchophen. A few duodenal ulcers occurred, but the majority of the ulcers were gastric. The use of bone as a mechanical irritant increased the rapidity of the formation of ulcer but did not demonstrably influence the rate of healing. Cinchophen administered by rectum, parenterally, through intestinal fistulas or orally to dogs which had fundic pouches produced peptic ulcer in all instances, which proved that ulcer occurred after absorption of the drug. The ulcer begins with an initial destruction of mucosal cells. The progression and healing are similar to those observed in other experimental peptic ulcer and in ulcer in man.

CEREBRIFORM NEVUS RESEMBLING CUTIS VERTICIS GYRATA

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The condition now known as cutis verticis gyrata was first described by Robert in 1848. The second example of this disease was recorded by Devergie (cited by Meirowsky) in his book "Traité pratique des maladies de la peau," which was published in 1854. In 1893 McDowell, an English neuropsychiatrist, described a similar case occurring in an epileptic microcephalic idiot. In the same year, Cowan reported 2 cases of the same nature, occurring in idiots. Jadassohn, at the Ninth Congress of the Dermatological Society in 1906, in Bern, presented a patient whose scalp in the occipital region was arranged in irregular folds, varying from 0.75 to 1.5 cm. in width. He later reported 2 additional cases. Unna in 1907 reported 3 cases of a similar nature. These cases were characterized by a gyrate appearance of the scalp over the vertex and the back of the head, resembling in appearance the furrows and convolutions of the cerebrum. He called the condition cutis verticis gyrata, and this name is the one most commonly employed today. Von Veress introduced the term "cutis verticis striata" to designate the 11 cases which were reported by him in 1908. In 1909 Audry introduced the name "pachydermie occipitale vorticellée" in describing his case. Stratton in 1933 found 158 cases reported by 87 different authors during a complete review of the literature on the subject.

GENERAL CHARACTERISTICS OF CUTIS VERTICIS GYRATA

Cutis verticis gyrata is a disease of the scalp characterized by the presence of a variable number of convolutions, or gyri, separated by furrows, or sulci. It is usually situated in the posterior parietal and occipital regions, although any portion of the scalp may be involved. The convolutions and furrows may be more or less parallel, running anteroposteriorly, from side to side or diagonally across. Less often they may be irregularly situated. The convolutions are permanent and ineffaceable, so that they can neither be made to disappear by traction on the skin nor be produced by pressure and counterpressure on the scalp. There are, in general, two main variables of this disease.

From the Department of Surgery, University of Michigan.

In the first type the gyri are less markedly elevated and merge imperceptibly into the adjacent normal scalp, a definite line of demarcation between the abnormal and the normal being absent. The maximum change is generally in the midline and extends symmetrically in all directions, becoming less and less marked as the periphery is approached.

The second type is characterized by a definite circumscribed tumor with raised abrupt borders. The convolutions in this type are more prominent and the furrows deeper, closely simulating the appearance of the cerebrum. The growth does not tend to be symmetrically situated. Another distinguishing feature is that it occurs more frequently in females and is usually present from birth. This type is caused by a nevus, usually of the pigmented variety. Slow growth is the rule, although periods of more rapid growth are not uncommon. Whereas the first type is usually inconspicuous and discovered accidentally, the second type forms a prominent tumor mass which is obvious to the patient for a long time.

ETIOLOGY AND CLASSIFICATION OF CUTIS VERTICIS GYRATA

For many years considerable confusion and disagreement existed in the minds of various authors concerning the exact etiology of cutis verticis gyrata. This was largely due to the fact that it was not generally recognized that this disease may be related to several different etiologic factors.

In 1893 McDowell suggested that the cutaneous folds were due to hypertrophic muscles of the scalp, similar to the folds noticed when a dog "pricked his ears." It seems reasonable to assume that in some cases cutis verticis gyrata represents a reversion to a period when the muscles of the scalp could move the scalp at will. Fischer (1922) expressed the belief that the anomaly in certain cases is developmental and is comparable to the conditions present in the scalps of many mammals, such as lions, tigers and bulldogs. The occurrence of cutis verticis gyrata in idiots tends to support these views.

Jadassohn in 1906 and Unna in 1907 regarded the condition as the result of an anomaly of development and classified their cases as belonging to the larger general group of nevi. This view was supported by Silvestri (1909) and Rouvière (1911). Malartic and Opin (1914) and Lenormant (1920) definitely established the nevic nature in their cases by histopathologic examination. Various inflammatory diseases of the scalp were considered as the etiologic agents by von Veress in 1908 and by Audry in 1909. In 1911 Sabat reported a case associated with acromegaly, and Adrian (1916) and Grönberg (1927) suggested a causal relationship between the two diseases. Galant (1918) and Stühmer (1922) expressed the belief that the condition in their cases had developed on a traumatic basis.

Von Veress (1908), Pospïeloff (1909) and Wise and Levin (1918) found cutis verticis gyrata associated with syphilis. It was not demonstrated by any of these observers that an actual syphilitic infiltration of the scalp was responsible for the abnormality, although a generalized syphilitic infection was present at the time the patients were first examined. Fischer in 1922 advanced the theory that in some cases the condition could be explained on the basis of an anomalous and apparently congenital hypertrophy of the connective tissue of the scalp. Oliver in 1922 offered the explanation that in time a chronic inflammatory process in the scalp produces fibrous tissue, which by contracting gives rise to furrowing of the scalp. Pelagatti (1924) described a case in which the anomaly was due to a leukemic infiltration of the scalp. Truffi (1930) reported a case in which pemphigus seemed the causative factor.

In 1933 Stratton argued that the anatomic construction of the scalp might explain the condition, since so many unassociated causes apparently resulted in the same deformity. He stated that in the scalp strong fibrous bands run diagonally and perpendicularly through the fat, firmly connecting the galea aponeurotica and the skin. It was conjectured that the fat was replaced by the infiltrating cells but that the fibrous bands were not. This resulted in gyri and sulci, or the formation of cutis verticis gyrata. He thought that the size of the gyri depended directly on the intensity of the infiltration.

Fischer (1922) greatly simplified the entire subject of cutis verticis gyrata by offering an etiologic classification which served to correlate the many conflicting views regarding etiology. His classification is as follows:

A. True cutis verticis gyrata—a developmental anomaly representing a reversion to a lower form of life when the muscles of the scalp could move it at will.

B. Diseases of the scalp "in the form of" cutis verticis gyrata.

1. Inflammatory changes, acute and chronic, e. g., eczema, psoriasis, folliculitis and impetigo.
2. Anomalous and apparently congenital hypertrophies of the connective tissue.
3. Tumors, such as nevi and neurofibromas.
4. Changes in the scalp occasioned by diseases that lead to proliferation of the tissues, such as acromegaly, myxedema, leukemia and cretinism.

To this classification might be added:

5. Changes in the scalp resulting from trauma.

In the present study, reports of 117 cases of cutis verticis gyrata were found in the literature. We have attempted to group these cases according to Fischer's classification. There were 9 cases of true cutis verticis gyrata, forming 8 per cent of the total. Eighty-five cases of diseases of the scalp "in the form of" cutis verticis gyrata were found, aggregating 72 per cent of the entire number. In 22 cases, or 19 per cent, the data given were insufficient to permit an accurate classification.

Of the 85 cases which fell into the second group, 26 (22 per cent) were caused by inflammatory changes; 4 (3 per cent) resulted from anomalous and apparently congenital hypertrophy of the connective tissue; 24 (21 per cent) were due to neoplasms, all of which were nevi; 26 (22 per cent) were occasioned by diseases that lead to proliferation of the tissues, and 6 (5 per cent) were consequent on trauma.

The 26 cases occasioned by diseases that lead to proliferation of the tissues have been further subdivided into 19 cases associated with acromegaly, 1 case caused by a leukemic infiltration of the scalp, 4 cases apparently due to syphilis and 2 cases in cretins.

HISTOLOGIC PICTURE OF CUTIS VERTICIS GYRATA

Naturally, the histopathologic picture of the disease will vary according to the etiologic agent.

We have found no observations on the histopathologic picture in cases of true cutis verticis gyrata or in cases of changes in the scalp in the form of cutis verticis gyrata resulting from trauma. Neither have we noted any observations concerning the histopathologic picture in cutis verticis gyrata occasioned by diseases that lead to proliferation of the tissues.

Von Veress (1908), Vignolo-Lutati (1910) and Hannay (1923) have reported their microscopic observations in cases of cutis verticis gyrata following inflammatory diseases of the scalp and, in general, their descriptions are in agreement. According to them, the epidermis exhibited no change. In the deeper parts, infiltrations of plasma, lymph and mononuclear cells could be seen, often localized about the deeper follicles. Von Veress reported a complete disappearance of elastic fibers. Atrophy of the sebaceous and sweat glands occurred in some cases, while von Veress found a disappearance of the sebaceous glands in his cases. No excessive pigment formation was seen.

The histopathologic picture in the group of cases caused by an anomalous and apparently congenital hypertrophy of the connective tissue is self-explanatory. Ota (1931) found hyperplasia of the sebaceous glands with a thickening of the connective tissue of the cutis.

Tumors in the form of cutis verticis gyrata have been described by various authors. Malartic and Opin (1914) and Lenormant (1920) saw large numbers of nevus cells beneath the epidermis as the characteristic feature in their cases. Alderson (1927) found dense collections of pigment in the upper layer of the corium and large whorls or cords of connective tissue in the lower layer. No nervous tissue was seen. Grieve and Biddle (1931) noted pigmented nevoid cells just beneath the epidermis. In their cases the connective tissue was very cellular and vascular and was arranged in concentric bundles or whorls, especially well marked in the deeper layers of the corium. Madden (1935) reported an unusual case of cutis verticis gyrata due to a melanoma which had undergone malignant degeneration.

ORIGIN AND NATURE OF THE NEVUS

For many years there has been a divergence of opinion as to the origin of the nevus. There are, in the main, two schools of thought on the subject. One considers the nevus to be of mesodermal origin, and the other, of ectodermal origin. Each theory has been strongly supported by recognized investigators.

It is of interest to review a more recent conception of the origin of the nevus because this view seems entirely plausible and is being more and more widely accepted today.

Soldan in 1899 observed the association of nevus cells with sensory nerve elements and advanced the opinion that the nevus, like a neurofibroma, was formed by proliferation of the connective tissue of the sensory nerves of the skin. The pigmentation was considered to be a consequence of this fibromatosis.

Recently, by special staining methods, Masson (1926, 1931, 1932 and 1933) presented convincing evidence to show that the nevus and the melanoma are formed not by an abnormal proliferation of the connective tissue of the nerve sheaths but by a proliferation of the ends of the cutaneous sensory nerves. He expressed the belief that in the dermis the nevus cells arise from the cells of Meissner's corpuscles; that in the epidermis they come from the specialized tactile corpuscles of Merkel-Ranvier, and that they originate from the special pigment cells known as chromatophores in both situations. He has observed many features of nevus formation in the pigmented spots in the skin in Recklinghausen's disease and has found miniature neurofibromas in connection with nevi. He, therefore, accepts the relation of the nevus to neurofibromatosis. It is Masson's opinion that all nevi are neuronevi and that all are neuromatous terminations of tactile nerves. This theory serves to harmonize the ectodermal and mesodermal theories of origin and is supported by Ewing (1928), Stout (1932), Foot (1932), Weller 1936) and many others.

TREATMENT OF CUTIS VERTICIS GYRATA

The treatment of this disease has depended greatly on the etiology and nature of the abnormality. No treatment has been advocated for those cases not caused by a nevus, except for the treatment of the underlying disorders such as inflammatory diseases, myxedema, acromegaly, etc. The literature contains no report of a cure of cutis verticis gyrata of this type after improvement or cure of the causative factor. As a rule, surgical treatment is not indicated, because, first, there is little demarcation between the normal and the abnormal scalp, so gradually does the one blend into the other; and, secondly, the patient does not desire radical treatment for a lesion causing so little inconvenience and deformity.

However, in those cases in which the condition is caused by a nevus, one is dealing with a circumscribed, deforming tumor which has malignant potentialities. As for a nevus elsewehere, the treatment is surgical. There are two types of procedure: (1) complete excision with subsequent skin grafting, if a primary closure cannot be effected, or (2) gradual partial excision with closure. The latter method was advocated by Davis in 1934 in the operative treatment of hemangioma.

Davis stated that this method is of value when the growth cannot be entirely removed at one operation with immediate primary closure, either because the defect is too large or because it is in a situation where there is insufficient lax tissue to allow an immediate closure. We have found it a worth-while method in treating a large nevus of the scalp. In this procedure an elliptic incision is made in the tumor, and as much of the growth as possible is removed, but not enough to interfere with immediate closure of the wound. According to Davis, after healing is complete, in order to allow stretching of the surrounding tissues, at least two months should elapse before the second operation. This is carried out in exactly the same manner, and the procedure is continued with similar intervals until the growth is completely eradicated. During the intervals massage is helpful in stretching the skin. The objection may be raised that the trauma caused by partial excision might possibly result in malignant degeneration. It is an alternative method that may be used in certain cases in which the condition does not lend itself to complete excision with subsequent primary closure or skin grafting.

In this discussion it is of interest to note the differences of opinion among different writers as to the most satisfactory form of treatment of a nevus. These methods of therapy range from the application of the electric needle, solid carbon dioxide, cautery, caustics, radium and liquid air to electrolysis, roentgen irradiation, endothermy, electrodesiccation and electrocauterization. We believe that the best form of treatment is complete surgical excision.

REPORT OF CASES

Two cases of cerebriform nevus of the scalp resembling cutis verticis gyrata have recently been observed at the University Hospital.

CASE 1.—H. K., a 9 year old white American school girl, was admitted to the clinic on July 25, 1933, complaining of a growth on the side of the head. This lesion had been present since birth and had been increasing in size recently. It caused her no discomfort, but the parents desired its removal for cosmetic reasons.

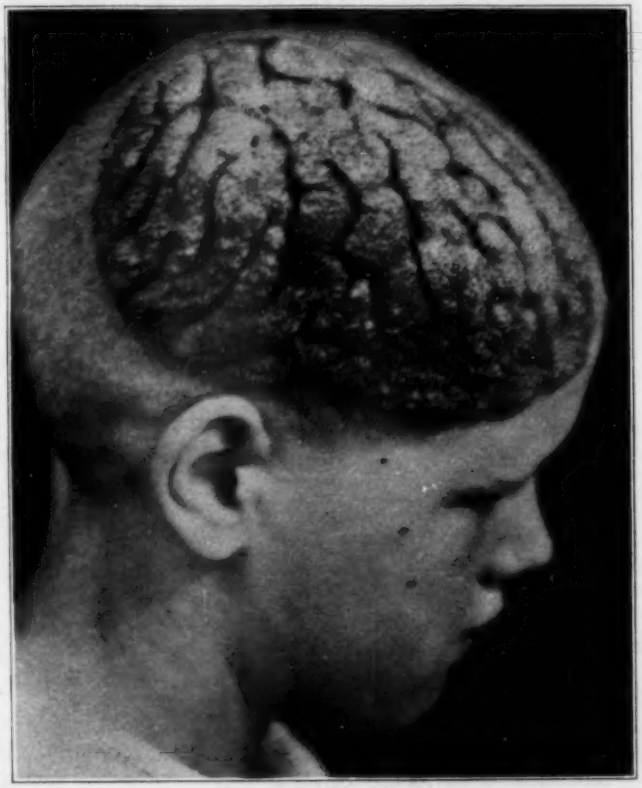

Fig. 1 (case 1).—Cerebriform nevus of the scalp resembling cutis verticis gyrata.

There was no history of any other disease of the scalp or of injury to the scalp. The patient had no other complaints.

Her past history was essentially irrelevant. There was no history of a similar deformity in either parent and no history of syphilis.

Physical examination revealed a healthy, well developed, well nourished girl of normal mentality. A circumscribed tumescence covered with hair presented itself on the right parietofrontal region of the scalp. It was approximately 15 cm. long and 12 cm. wide and extended from the vertex to within 1 inch (2.5 cm.) of the right ear and from the occipital region posteriorly to the hair line of the forehead

anteriorly. This tumor was composed of multiple gyri separated by rather deep furrows and was distinctly demarcated from the surrounding scalp by its raised abrupt edges. The gyri were rather soft and closely resembled cerebral convolutions. One portion of the growth exhibited a violaceous color. The tumor was not attached to the underlying bone. There was no evidence of inflammatory disease of the scalp. Whitish particles the size of a pinhead were attached firmly to the hair (figs. 1 and 2).

The remainder of the physical examination revealed nothing significant.

The results of the laboratory examinations were negative. The hemoglobin content was estimated to be 80 per cent (Sahli); the leukocytes numbered 6,400 per cubic millimeter. The urine was normal, and the Kahn reaction of the blood was negative. Roentgen examination of the skull revealed no bony abnormality.

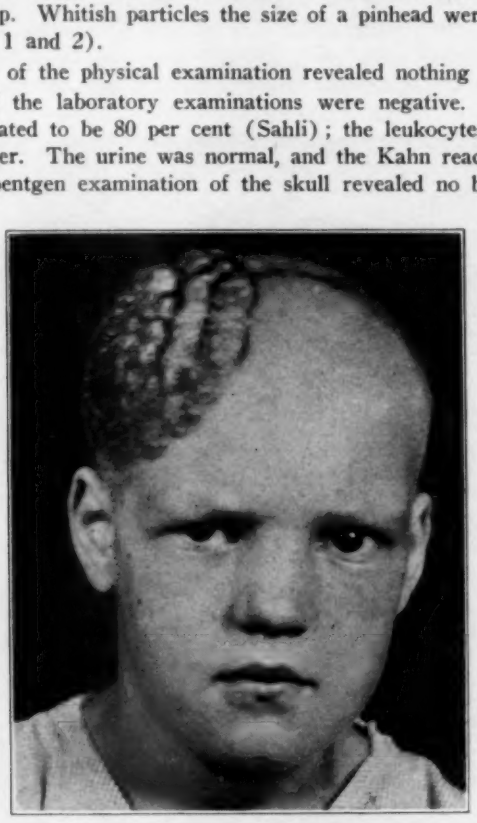

Fig. 2 (case 1).—The nevus as seen from the front.

Diagnoses of pigmented nevus of the scalp and pediculosis capitis were made, and surgical excision was advised.

Accordingly, on August 10, with the patient under anesthesia with tribromethanol in amylene hydrate and nitrous oxide curved vertical incisions were made through the central portions so as to excise an ellipse of the tumor. The tumor tissue showed no unusual vascularity. The edges of the tumor were then mobilized and sutured together with black silk, obliterating the operative defect. The tumor tissue removed measured 15 by 6.5 cm. Convalescence was uneventful. The wound healed by primary intention, and the patient was discharged on September 2.

She was readmitted to the hospital on November 11. The history for the interval between discharge and admission was unimportant. Examination revealed no change in the character of the tumor except for the diminution in size, resulting from the first partial excision. On November 11, with the patient anesthetized

with tribromethanol in amylene hydrate and nitrous oxide, an elliptic sagittal incision was made through the temporal part of the mass, extending down to the pericranium. The ellipse of tumor was then removed. The edges of the skin were approximated without undue tension and sutured with interrupted black silk. This portion of the tumor measured 15 by 3 cm. The postoperative course was without event, and the patient was discharged on December 1.

She returned on June 12, 1934, giving an unimportant history for the interval between discharge and admission. Examination gave negative results, except for the presence of the remaining portion of the tumor. On June 16, the same type of anesthesia being used as before, a narrow elliptic incision was made in the sagittal direction of the scalp, and the remaining portion of the tumor was excised. The edges of the skin were mobilized and closed without undue tension with black

Fig. 3 (case 1).—The operative scar and areas of hyperpigmentation in the surrounding skin. These cannot be seen when the hair is dressed naturally.

silk. This portion of the tumor measured 15 by 3 cm. The convalescence was entirely satisfactory, and the patient left the hospital on June 27.

A check-up examination on August 22 revealed an excellent result.

The patient was last seen on March 20, 1935 (fig. 3). There was no indication of recurrence, and the result was satisfactory. The scalp in the region of the operative scar revealed areas of hyperpigmentation, which disappeared at the hair line and were not visible when the hair was normally dressed.

The histopathologic description of the excised tissue was as follows (Dr. C. V. Weller): "The highly convoluted scalp is covered by an atrophic squamous epithelium beneath which there are many nests of typical nevus cells, producing large amounts of melanin. In the deeper portions, the proliferation assumes a pronounced fibroblastic character with a whorling architecture, so that, in many fields,

the appearances are those of a typical neurofibroma with all the intervening nevoid gradations being demonstrable. In the neurofibromatous portion, no melanin production occurs. This is a pigmented nevus, showing very beautifully the combination of neurofibromatous areas and medullary nests of nevus cells" (fig. 4).

CASE 2.—M. L., a 22 year old white American woman, was admitted to the University Hospital on May 29, 1934, complaining of a tumor on the back of her head and swollen glands in the neck. The growth had been present since infancy and had slowly increased in size. Two months before entrance to the hospital the growth had become painful, and she had noted chills and fever. She thought that one portion of the tumor had become infected and had "drained" for a short time.

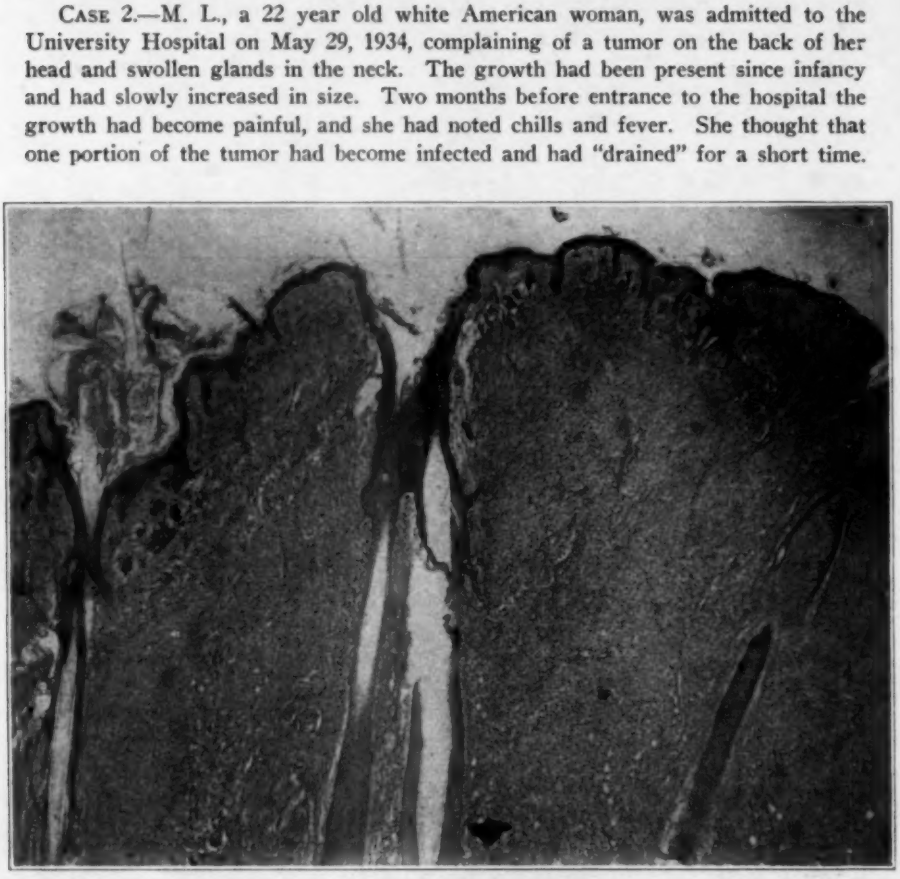

Fig. 4 (case 1).—Superficial medullary nests of nevus cells producing melanin and more deeply situated neurofibromatous areas (× 24).

At that time the glands of the right side of the neck had become tender and swollen and had remained in that condition. Her history was otherwise noncontributory. There was no history of syphilis, inflammatory disease of the scalp or trauma to the scalp. The patient had been overweight for many years.

Physical examination revealed a very obese white woman, appearing the stated age of 22 and having a normal mentality. There was an unusual tumor situated in the posterior portion of the scalp. It was an elevated, circumscribed growth, roughly circular in outline, extending from the vertex to the lower occipital region, posteriorly and to within 1 inch of either ear laterally. It was orange-red and measured 25 cm. in its greatest vertical diameter and 20 cm. in its greatest horizontal diameter. The surface was elevated 2 cm. above the surrounding scalp.

It presented many rubbery, firm nontender nodules and convolutions separated by furrows which, in part, greatly resembled convolutions of the cerebrum. The hair was rather thick in the sulci and sparse over the surface of the convolutions. The tumor was movable over the underlying skull. No inflammation was present. The cervical lymph nodes in the right anterior and posterior triangles were slightly enlarged and tender (fig. 5). The remainder of the physical examination revealed nothing significant. The examinations of the blood and urine gave essentially negative results. The Kahn test of the blood was negative.

Diagnoses of nevus of the scalp and obesity were made.

Due to the depth and firmness of the convolutions in various parts of the tumor, complete excision with subsequent skin grafting seemed to be the procedure of

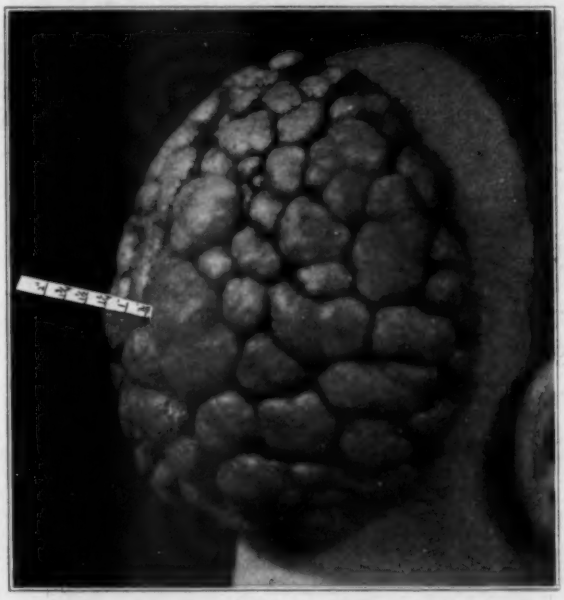

Fig. 5 (case 2).—Cerebriform nevus of the scalp resembling cutis verticis gyrata.

choice. Therefore, on June 4, the patient being anesthetized with tribromethanol in amylene hydrate and nitrous oxide, a circular incision was made about the periphery of the tumor, which was then elevated. A definite line of cleavage was found in the subaponeurotic space, and the tumor was thus easily removed. The edges of the skin were sutured to the pericranium to prevent retraction. Bismuth tribromphenate was used in dressing the wound (fig. 6). The convalescence was uneventful. On June 23, with the patient under nitrous oxide anesthesia, split thickness skin grafts were taken from the posterior aspect of the right thigh and applied to the denuded area on the posterior aspect of the scalp by suturing them to each other and to the surrounding skin. A sea-sponge pressure dressing was applied. The grafts were successful (fig. 7). The donor areas on the thigh were epithelialized completely in about twelve days. The patient was discharged from the hospital on July 28.

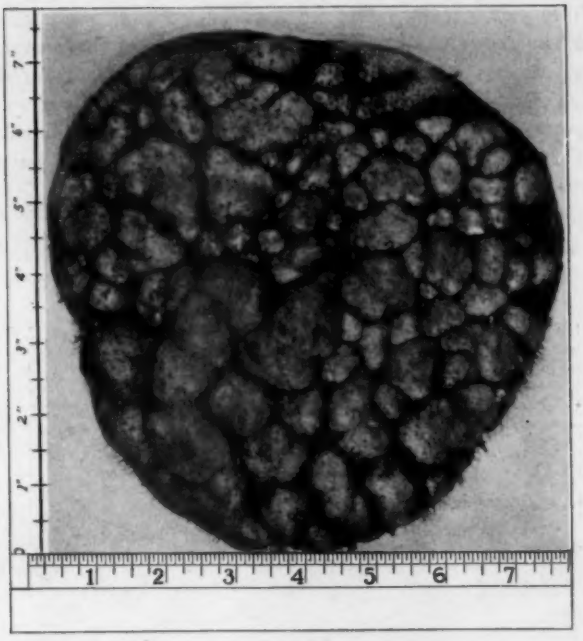

Fig. 6 (case 2).—Appearance of the nevus after its removal.

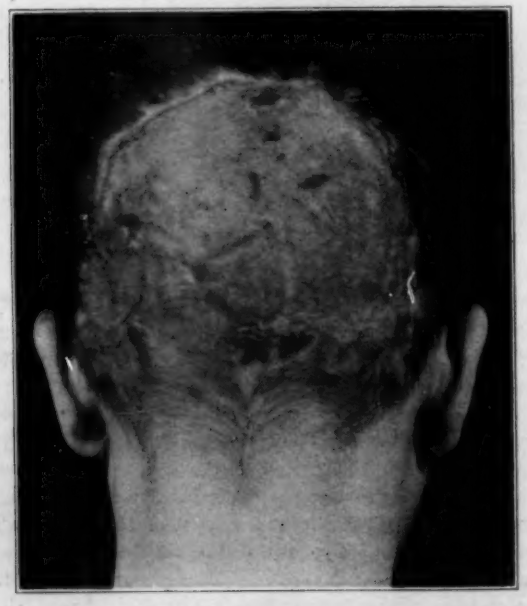

Fig. 7 (case 2).—The operative defect covered by skin grafts.

Fig. 8 (case 2).—Photomicrograph of the nevus (× 24).

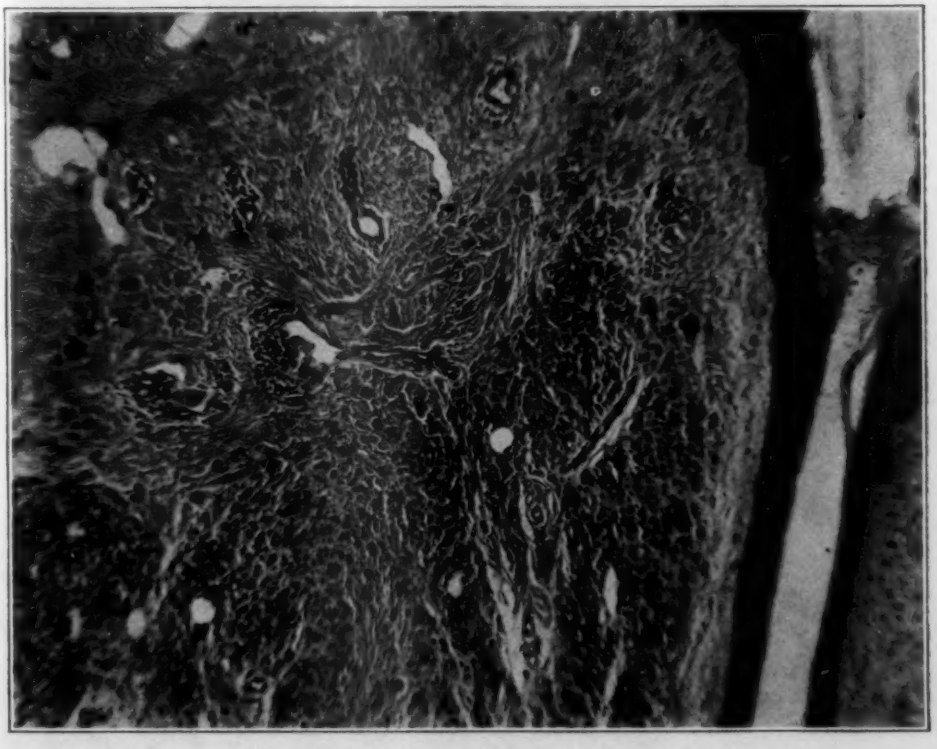

Fig. 9 (case 2).—Photomicrograph showing the nevus cells close beneath the epithelium (× 110).

On March 15, 1935, she reported by letter that she was well and that there had been no sign of recurrence.

The histopathologic description of the neoplastic tissue was as follows (Dr. C. V. Weller): "The scalp is thrown into convolutions by a marked thickening of the corium. There is a widespread proliferation of nevus cells, many of which grow in small nests and cords close beneath the papillomatous squamous epithelium. In the deeper portions, the proliferation assumes a markedly fibroblastic character, whorls of stroma containing elongated cells with spindle-shaped and ovoid nuclei being prominent. In these regions, the appearances suggest those of a neurofibroma" (figs. 8, 9 and 10).

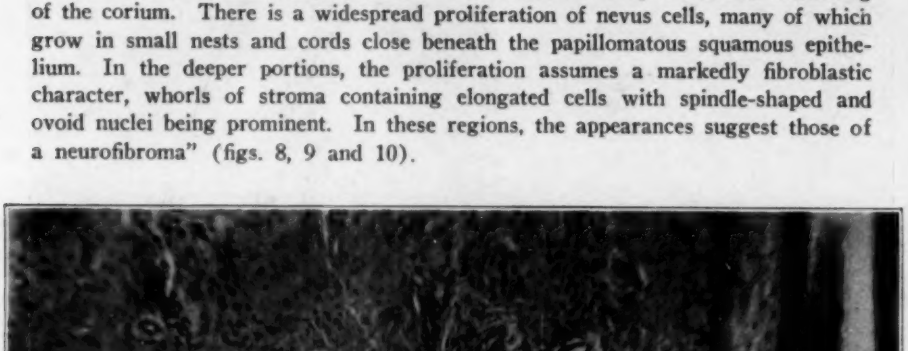

Fig. 10 (case 2).—Photomicrograph of a deeper portion showing the neurofibromatous areas (× 110).

COMMENT

As already indicated, the particular nevus of the scalp reported here constitutes a condition distinctly different, both clinically and pathologically, from all the other types of cutis verticis gyrata. Since this condition presents so few features in common with cutis verticis gyrata, we suggest that it be removed from this classification and designated as cerebriform nevi of the scalp. An interesting commentary in this connection is the fact that in the literature and textbooks this convoluted nevus is referred to as cutis verticis gyrata when it occurs on the scalp,

but as nevus cerebriformis or cerebelliformis when it occurs elsewhere on the surface of the body.

As suggested by Madden (1935), cutis verticis gyrata should be considered a descriptive term only, and it should be generally understood that several different pathologic processes in the scalp may result in the formation of convolutions and furrows. In any patient exhibiting cutis verticis gyrata, a careful differential diagnosis should be made to determine the underlying cause so that appropriate treatment can be recommended.

We believe that Masson has shown rather conclusively that a nevus represents a proliferation of the chromatophores, tactile corpuscles and nerve cells, forming the end-apparatus of the sensory nerve filaments of the skin. There seems to be little doubt of the relationship of the nevus to the neurofibroma. The results of the histopathologic study in the 2 cases herein reported support Masson's concept of the neurogenic nature of the nevus.

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FRACTURES OF THE ANKLE

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During the period from 1932 to 1934 there were admitted to the fracture service for females at the Cook County Hospital patients with 3,294 fractures. The fractures, dislocations and tears in the ligaments of the ankle numbered 352, or 10.84 per cent of all fractures. These were reduced and treated subsequently in the follow-up clinic. Our data are based on the records of the hospital and the follow-up clinic and on our study of 300 of the hospital's roentgenograms.

We are adding to these data the results of a study of 78 fractures of the ankle encountered in private practice, with a review of the roentgenograms. Our work, therefore, is based on a study of 430 fractures of the ankle and a review of the roentgenograms of 378.

The clinical study of these fractures has been augmented by a detailed description of the practical anatomy and physiology of the ankle joint by one of us (L. B.).

Even after employing the accepted methods of treatment of Pott's fracture and other injuries to the ankle, the results, such as faulty weight bearing, pes planus, limitation of motion, widening of the mortise and arthritic and circulatory changes, have motivated the study.

We propose to clarify confusion in the classification, anatomy and mechanism and to advocate an additional manipulation in the reduction of fractures with dislocation.

ANALYSIS OF DATA

The incidence of fractures of the ankle at the Cook County Hospital for the three year period was as follows:

	Total Fractures	Fractures of the Ankle	Percentage
1932	1,024	95	9.5
1933	1,070	99	9.2
1934	1,155	158	14.0
	3,249	352	10.84

On the basis of the type of fractures we classified the 300 fractures studied roentgenographically as follows:

	No.	Percentage
Pott's fracture (figs. 8, 9, 12, 13, 14, 15, 16, 17 and 22)	225	75.0
Supination fracture (fig. 19)	15	5.0
Bimalleolar fracture (fig. 10)	28	8.5
Solitary marginal fracture	3	1.0
Compression fracture (fig. 11)	5	1.6
Simple fracture (fig. 20)	21	7.3
Epiphysial separation (fig. 18)	3	1.0

We further subdivided the fractures of the ankle as follows:

A. Pott's fracture			225
Uncomplicated (figs. 8, 9, 15, 16, 17 and 22)		157	
With a Tillaux fragment (small marginal fracture)		27	
Anterior (fig. 14)	1		
Posterior (fig. 15)	24		
Anterior and posterior	2		
Anterior marginal		6	
Posterior marginal (fig. 12)		30	
Anterior and posterior marginal (fig. 23)		5	
B. Supination fracture			15
Uncomplicated (fig. 19)		9	
With a Tillaux fragment (posterior)		1	
Anterior marginal		2	
Posterior marginal		0	
Anterior and posterior marginal		1	
With fracture heads of the fibula		1	
With epiphysial separation		1	
C. Bimalleolar fracture (fig. 10)			28
Uncomplicated		20	
With a Tillaux fragment		0	
Anterior marginal		1	
Posterior marginal		6	
With epiphysial separation		1	
D. Solitary marginal fracture			3
Anterior		0	
Posterior (2 without dislocation)		3	
E. Compression fracture (fig. 11)			5
F. Simple fracture one or both maleoli (without any dislocation)			21
External malleolus (fig. 20)		17	
Internal malleolus		3	
External malleolus and anterior marginal		1	
G. Epiphysial separation (fig. 18)			3

In the roentgenograms of 300 fractures of the ankle we noted the following involvement of the bones:

External malleolus	150
Internal malleolus	109
Both malleoli	57
Fibula, above the joint	183
Oblique fracture of the fibula	153
Posterior marginal fragment	39
Anterior marginal fragment	9
Both Tillaux and marginal fragments	63
Tillaux fragment (posterior)	27
Both anterior and posterior marginal fragments	3

It is interesting to note the following facts:

1. Pott's fracture occurred in 75 per cent of our series but was complicated by some form of marginal fragment in 30 per cent. We consider this complication higher in females than in males, probably because the former wear high heels.

2. Solitary marginal fracture is uncommon, occurring only 3 times in 300 roentgenograms and from our records of 352 cases. This is less than 1 per cent of fractures of the ankle. In only 1 of these was there a posterior dislocation, so that 2 of these might have been classified as simple fractures.

3. The most common fracture was Pott's fracture, in which there is an oblique and sometimes a spiral fracture of the fibula running downward and forward. This constituted 50 per cent of all our fractures. It is the most common fracture of the ankle. In about 10 per cent of these there was also involvement of the external malleolus.

4. In supination or fractures with medial dislocation, we noted in addition to fracture in the fibula or external malleolus a longitudinal fracture of the tibia or a spiral fracture in the shaft of the tibia.

The incidence of dislocations was as follows:

Lateral dislocation	157
Posterior dislocation	45
With lateral and posterior dislocation	36
Upward dislocation (compression)	5
No dislocation	21
Reduction of fracture before taking roentgenogram (mostly Pott's fracture)	36
Diastasis noted roentgenographically	117

The clinical facts in this series of fractures are summarized briefly:

The time of fixation for uncomplicated Pott's fracture averaged five and one-half weeks; for lateral and posterior displacement, seven weeks; for all types, six weeks.

Two or more reductions were required in 30 cases.

There were 6 compound fractures. In 2 of these cases extension on a Braun or Böhler splint was used.

Extension with a Kirschner wire or a Steinmann pin was used 6 times.

The length of time before weight bearing was allowed averaged in all cases about ten weeks; for uncomplicated Pott's fracture, eight weeks; for Pott's fracture or bimalleolar fracture with posterior dislocation, eleven weeks; for posterior marginal fractures, eleven and one-half weeks.

Results were markedly good in 168 fractures, fair in 33, poor in 15 and undetermined in 84. These data depend entirely on the examiner's opinion. Measurements made by one of us on 50 fractures of the ankle showed an increase in the circumference of the ankle at the malleoli in 47. Note that in 300 roentgenograms diastasis was found in only 117, or 40 per cent, whereas widening of the mortise was observed in 94 per cent as a clinical end-result. In many of these there was pes planus, and in many others the roentgenograms showed fairly good position.

In reviewing the films and records of 78 cases encountered in private practice, we note the following distribution of fractures:

	No.	Percentage
Pott's fracture	38	49.0
Supination	2	2.5
Bimalleolar fracture	6	7.0
Solitary marginal fracture	2	2.5
Compression fracture	1	1.3
Simple fracture	29	37.0
Epiphysial separation	0	0.0

In this series, as compared with those at the Cook County Hospital, there were more uncomplicated Pott's fractures and more simple fractures. In the 2 posterior marginal fractures there were no posterior dislocations.

In looking over the films we found a single instance of injury to the ankle, clinically accompanied by swelling and pain but no fracture. There were, however, considerable diastasis and widening in the mortise. We found no cases of dislocation without fracture. Diastasis probably occurs in many cases of sprain and is a cause of later disability.

There were 21 multiple fractures in our series.

ANATOMY AND PHYSIOLOGY OF THE ANKLE JOINT

Only such anatomic points will be presented as bear on our views of the mechanism of fractures of the ankle.

Inferior Tibiofibular Syndesmosis.—The distal extremities of the tibia and fibula articulate by surfaces which are for the most part rough

and bound together by ligament, but at the distal part, for a distance of about ¼ inch (0.6 cm.), they are separated by a cleft, continuous with the cavity of the ankle joint, which is lined by synovial membrane and commonly contains a synovial fold.

The ligaments of this articulation are: 1. The anterior lateral malleolar (anterior inferior tibiofibular) ligament (fig. 1). This ligament extends obliquely downward and outward, is about ¾ inch (1.9 cm.) wide and is attached to the external and anterior angle of the lower extremity of the tibia; it is attached to the fibula along the

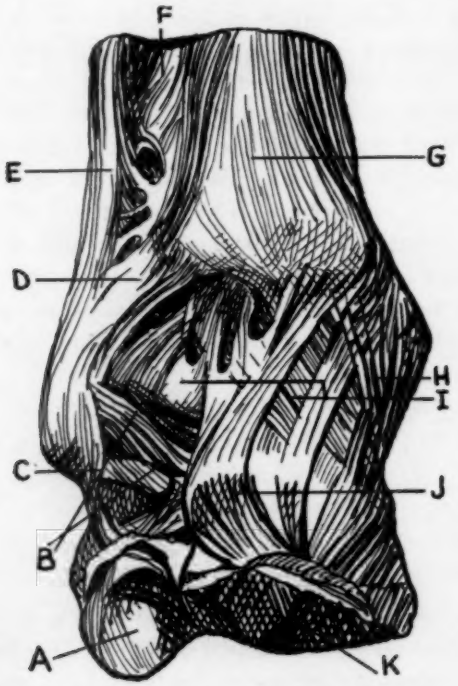

Fig. 1.—Anterior view of the ankle joint (modified after Bourgery: Traité complete de l'anatomie de l'homme comprenant de la médicine operatoire, Paris C.-A. Delaunay, 1832-1854). *A* indicates the calcaneum; *B*, two bands of the anterior talofibular ligament; *C*, the exterior lateral ligament; *D*, the anterior inferior tibiofibular ligament; *E*, the fibula; *F*, the interosseous ligament; *G*, the tibia; *H*, the internal lateral ligament; *I*, the anterior ligament of the ankle joint; *J*, a prominence formed by the astragalus, and *K*, the scaphoid.

lower ½ inch (1.3 cm.) of the ridge in front of the superficial triangular surface of the bone; to the anterior surface of the malleolus, nearly down to the anterior portion of the external lateral ligament of the ankle, and to a part of the anterior ligament of the ankle. The fibers of the ligament increase in length from above downward.

2. The posterior lateral malleolar ligament (fig. 2). This ligament extends from the external angle of the posterior surface of the lower end of the tibia, downward and outward to the fibula, along the lowest ½ inch (1.3 cm.) of the ridge separating the posterior from the external surface and to the upper half of the posterior border of the external malleolus.

3. The transverse ligament (fig. 2). The posterior lip of the tibial plafond projects so low as to have been called by Destot the posterior malleolus. The transverse tibiofibular ligament, located beneath

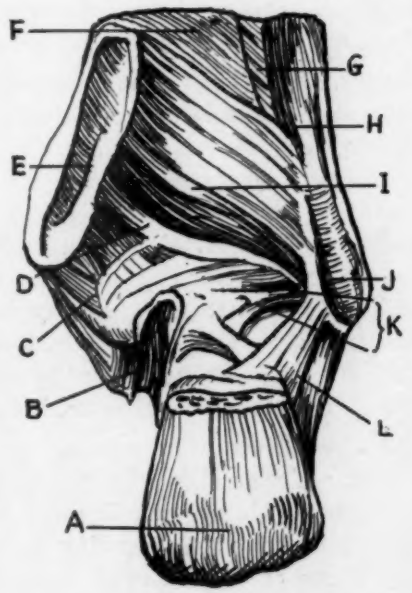

Fig. 2.—Posterior view of the ankle joint (modified by Bourgery). *A* indicates a posterior tubercle of the os calcis; *B*, a groove on the astragalus for the flexor hallucis longus tendon; *C*, the internal lateral ligament; *D*, the transverse ligament; *E*, a groove for the flexor digitorum longus and the tibialis posterior tendons; *F*, the tibia; *G*, the inferior interosseous ligament; *H*, the fibula; *I*, the posterior inferior tibiofibular ligament; *J*, a groove for the peroneus tendons; *K*, the posterior fasciculi of the external lateral ligament, and *L*, the middle fasciculus of the external lateral ligament.

the posterior inferior tibiofibular ligament, extends from the posterior lip of the tibia to the posterior and inner angle of the base of the external malleolus. Another way of describing this ligament is that the distal part of the posterior inferior tibiofibular ligament forms a strong band, which takes a transverse course and is firmly attached to both the tibia and the fibula. It constitutes a part of the tibiofibular

socket for the talus at the ankle joint and is sometimes called "the distal ligament of the lateral malleolus."

4. The inferior interosseous ligament (figs. 1 and 2). This ligament consists of a dense mass of short fibers, passing transversely between the opposed lower ends of the tibia and the fibula, except for ⅜ inch (0.9 cm.) at the extremity of these surfaces, where there is a synovial cavity. The ligament extends from the anterior to the posterior inferior tibiofibular ligaments. In front it reaches upward for 1½ inches (3.8 cm.), but behind, only about half that height.

The synovial cavity of this articulation communicates with that of the ankle joint. It is semilunar, with its convexity upward, where it is limited by the lower end of the inferior interosseous ligament.

The Ankle Joint Proper.[1]—This is a hinge joint, and the distal extremities of the tibia and the fibula are united so as to form a three-sided socket, which receives and embraces the talus. The socket is completed opposite the interval between the tibia and the fibula by the lower part of the anterior lateral malleolar ligament (mentioned previously) in front and by the transverse ligament behind. It is broader in front than behind, and its posterior margin is placed on a lower level than the anterior margin. An irregular archway is thus formed by the two bones of the leg, under which is received the astragalus, the outer buttress, which is the longer, being formed by the fibula, while the inner buttress and the span of the arch are formed by the tibia.

Ligaments of the Ankle Joint.—A capsular ligament invests the joint; it is thin in front and behind but is supported on each side by strong collateral ligaments. This capsular ligament, being attached in places beyond the astragalus, assists in forming the capsules of some of the tarsal joints. There are four named ligaments: the anterior, posterior, internal and external lateral.

The anterior and the posterior ligaments need no description.

The internal lateral ligament [2] (fig. 3), erroneously named the deltoid ligament, is a quadrilateral mass of vertical, coarsely fasciculated fibers, descending from the tibia to be attached posteriorly to the astragalus and anteriorly to the sustentaculum tali. The anterior part of this ligament is strengthened by fascia (partly derived from the internal annular, or laciniate, ligament), which fashions it into a deltoid structure. After reaching the sustentaculum tali, the true ligamentous fibers interlace with the upward and forward passing fibers of the supero-internal calcaneonavicular ligament.

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1. Lovett, R. W., and Cotton, F. J.: Some Practical Points in the Anatomy of the Foot, Tr. Am. Orthop. A. **11**:298-315, 1898.

2. Smith, E. Barclay: The Astragalo-Calcaneo-Navicular Joint, J. Anat. & Physiol. **30**:397, 1895-1896.

The external lateral ligament (fig. 4) consists of three parts. (*a*) The anterior portion is connected with the anterior border of the external malleolus just below the point of attachment of the anterior ligament of the ankle. Below it is fixed to the astragalus in front of the facet for the fibula. (*b*) The middle fasciculus is attached to a portion which passes as a groove round the inferior border of the external malleolus, slightly in front (but not to the tip), and passes downward to a tubercle on the outer surface of the os calcis. (*c*) The posterior fasciculus, probably the strongest of all, is attached at one end to the border of the external malleolus, which separates the peroneal groove

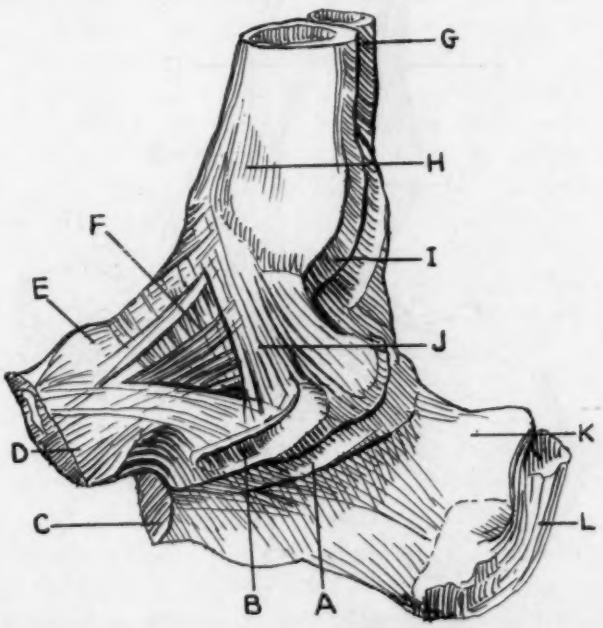

Fig. 3.—Medial aspect of the ankle joint (modified after Bourgery). *A* indicates the groove for the flexor digitorum longus and the flexor hallucis longus tendons; *B*, the groove for the tibialis posterior tendon; *C*, the calcaneus; *D*, the scaphoid; *E*, the astragalus; *F*, parts of the internal lateral and anterior ligaments of the ankle joint; *G*, the fibula; *H*, the tibia; *I*, the groove on the tibia for the flexor digitorum longus; *J*, the interior lateral ligament; *K*, the calcaneum, and *L*, the tendo Achilles.

from the fossa on the inner surface, and slightly to the lower part of the fossa itself, and at the other end to the rough outer surface of the astragalus below and to the articular facet for the fibula behind and also to the posterior external tubercle of the astragalus. This groove and depression for the posterior fasciculus constrict and weaken the bone. In accidents, because of the enormous strength of this pos-

terior fasciculus, holding the astragalus almost indissolubly attached to the external malleolus, either the fibula gives way, which is usual, or the posterior tubercle of the astragalus is detached. This lateral tubercle of the posterior process of the astragalus, or os trigonum, is present as a distinct bone or additional ossifying center in 7 or 8 per cent of cases. It is located from 5 to 7 mm. posterior to the median tubercle and is the portion of the astragalus which casts the farthest posterior shadow in lateral roentgenograms of the foot.

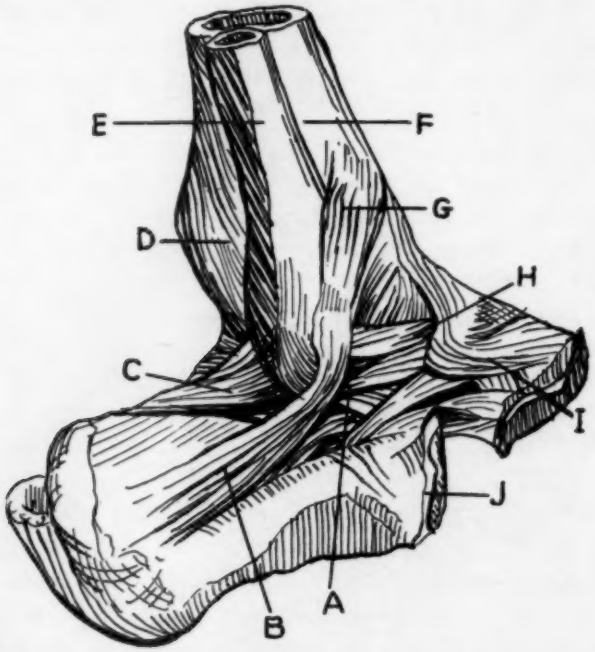

Fig. 4.—Lateral view of the ankle joint (modified after Bourgery). *A* indicates two bands of the anterior talofibular ligament; *B*, the middle fasciculus of the external lateral ligament; *C*, the posterior band of the external lateral ligament; *D*, the tibia plus part of the posterior inferior tibiofibular ligament; *E*, the fibula; *F*, the tibia; *G*, the anterior inferior tibiofibular ligament; *H*, the anterior band of the exterior lateral ligament; *I*, the scaphoid, and *J*, the calcaneum.

The synovial membrane of the ankle joint is extensive. It lines all the ligaments and sends upward a short cul-de-sac for the inferior tibiofibular joint. On the anterior and posterior surfaces it extends beyond the limits of the articular facets. The epiphysial line of the tibia is ½ inch (1.3 cm.) above the level of the ankle joint in front and about ⅝ inch (1.5 cm.) above posteriorly, so that the synovial membrane does not reach this line on either aspect. The epiphysial line of the fibula is from ¾ to ⅞ inch (1.9 to 2.1 cm.) above the tip of

the external malleolus and is almost 1 cm. below that of the tibia, lying in a direct horizontal line with the opposed articular surfaces of the tibia and the astragalus. This epiphysis, then, lies almost exactly on a level with the plane of the ankle joint. The synovial membrane overlaps the diaphysis of the fibula for about 0.5 cm.

Bony Configuration.—(*a*) Lower End of the Fibula: The external malleolus supports the ankle joint on the outer side, projecting down and more posterior than the internal malleolus. The result of this is that the foot may receive, in the best possible way, shocks transmitted to it from above.

(*b*) Shaft of the Tibia: This part of the bone is twisted; when the tibia is placed on its posterior surface it rests on the posterior edges of both its condyles but on the posterior and lateral edges only of its lower articular end, the inner malleolus being turned away from the supporting surface. This twist in the tibia gives an outward slant to the foot from the heel, causing the great toe to incline away from that of the opposite side when the heels are placed in contact. A line drawn from the point of the heel through the middle or longest toe coincides with the plane in which the foot moves in flexion and extension on the leg. The direction of this movement, therefore, is oblique with regard to that of the knee joint and to that of the plane in which the leg bones descend from the knee. The movement of the ankle joint takes place in a perpendicular plane on an axis, which passes from left to right through the lower part of the astragalus and which is the center of a circle of which the upper articular surface of the astragalus forms a segment.

(*c*) Astragalus: The whole of the upper, outer and inner surfaces and the greater part of the posterior surface of this bone assist in forming the ankle joint, either by smooth cartilaginous facets for articulating with the bones of the leg or by rough surfaces for the attachment of the ligaments. Of the three facets, we shall consider the superior only for our present purpose. This occupies the posterior two thirds of the upper surface of the bone; it is arched considerably, being decidedly narrower behind than in front and longer on the inner than on the outer side; the outer border is higher and more prominent, especially in front, so that there is a slight inward obliquity given to this upward looking facet.

From this description the fact can be appreciated that in extreme extension, or plantar flexion, there is a twisting of the toes inward and that is partly due to: (1) the greater posterior length of the inner border of the superior articular surface of the astragalus; (2) the lesser proportionate height posteriorly of the outer border of that

surface, the hindmost part of which is in plantar flexion brought into the tibiofibular arch, and (3) also partly the lateral movement in the calcaneo-astragaloid joints.

The movements of the foot on the leg are varied and difficult to analyze, because they pass easily into one another; because, as Humphry [3] stated, two or more are generally combined, and because they are divided between three distinct joints. These are (1) the joint between the tibia, fibula and astragalus; (2) the joint between the astragalus and the os calcis, a double joint having two separate synovial cavities, and (3) the joint between the first and the second row of tarsal bones—between the astragalus and the os calcis behind and the scaphoid and the cuboid bone in front—which is also a double joint.

Flexion and extension at the ankle joint take place around a transverse line drawn through the body of the astragalus. The movements are not in a direct anteroposterior plane but along a plane inclined outward and drawn through the foot from the middle of the astragalus to the opposed surfaces of the bases of the second and third metatarsal bones. This oblique plane corresponds to the outward inclination of the toes, to the slight twisting of the shaft of the tibia and to the posterior position of the external malleolus. For the sake of brevity we may say that the axis of movement of the ankle joint passes approximately through the end of the fibular malleolus. Thus the middle fasciculus of the external lateral ligament can be more or less tense throughout the range of movement, but the anterior and posterior fasciculi, being attached to the fibula away from the axis, are of more value in limiting movement and become tense in plantar flexion and dorsiflexion, respectively.

There is a slight lateral movement of the foot in ordinary plantar flexion, owing partly to the fact that the internal malleolus is shorter than the external and partly to the narrower end of the astragalus being in that position brought into the widest part of the intermalleolar notch.

Muscles Acting on the Ankle (Directly or Indirectly).—It is well known that no single muscle can produce simple flexion or extension of the foot without producing abduction or adduction at the same time.

1. The gastrocnemius and the soleus (spoken of together as the triceps surae) are the extensor-adductor muscles. They act by stretching the back part of the foot and the outer half of the forepart of the foot; they act in the plane of movement of the ankle by means of the tendo Achillis, which plane may, for simplicity, be said to be passing through the os calcis, the middle of the ankle joint and the space between the two inner metatarsal bones.

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3. Humphry, G. M.: A Treatise on the Human Skeleton (Including the Joints), Cambridge, Macmillan & Co., 1858.

2. The peroneus longus is the extensor-abductor muscle; the action of this muscle, combined with that of the triceps surae, causes direct extension of the foot at the ankle.

3. The tibialis anticus is the flexor-adductor muscle.

4. The extensor digitorum longus is the flexor-abductor muscle; the action of this muscle, combined with that of the tibialis anticus, causes direct flexion of the foot.

5. The tibialis posticus is a pure adductor muscle.

6. The peroneus brevis is a pure abductor muscle.

However, as pointed out by Cyriax (1917), Haines (1935) and others, some muscles have full action and others short action; the latter are those in which the length of the fibers is so short that they do not remain taut throughout the full range of movement permitted by their attachments; these include the biceps femoris, semimembranosus, rectus femoris, gastrocnemius, plantaris and soleus muscles. For example, when the ankle is in full plantar flexion and the knee is also flexed, the lower part of the leg not touching the ground, the tendo Achillis is slack to palpation. The only active muscles appear to be the tibialis posticus and peroneus muscles.

NOMENCLATURE OF THE MOVEMENTS OF THE ANKLE AND FOOT

There is a good deal of diversity of opinion concerning the nomenclature of the movements of the ankle and foot. We fully concur with the contention of Professor Thane,[4] who claimed that although the foot in the position of rest is more or less at right angles with, and projects both in front of and behind, the bones of the leg, the two projections are not of equal value. The axis of the limb is continued in the anterior projection, and the projection of the heel is a secondary prominence, which does not occur in the primitive form. The angle between the leg and the forepart of the foot is, therefore, the angle to be considered. A diminution of this angle is flexion, and an increase of this angle is extension, in accordance with what would universally be understood by "straightening the foot upon the leg." The terms flexion and extension are physiologic terms, and it is desirable that they should be used only in a physiologic sense. The direction at which the bending at a given joint takes place is determined by the functional requirements of the part. In the upper limb all the joints are bent in the same direction, in accordance with the use of the limb as a grasping organ. In the lower limb the large joints are bent in

4. Thane, G. D., in discussion on Humphrey, G. M.: J. Anat. & Physiol. **28**:xv-xvi, 1893-1894.

opposite directions alternately, that arrangement being the most convenient for the shortening of a column of support. We therefore conclude with most authorities that plantar flexion is extension of the foot and dorsiflexion, flexion of the foot.

Other movements are described in connection with the ankle and foot; these, however, belong not to the ankle but to the subastragaloid joints.

The movements of pronation of the foot consist of the horizontal rotation of the astragalus with the sinking of its head, the rotation in valgus of the os calcis beneath it and the rotation in valgus and abduction of the front part of the foot as a whole, occurring between the astragalus and the scaphoid and between the os calcis and the cuboid bone. The head of the astragalus moves in a ball and socket joint formed by the sustentaculum tali, the calcaneoscaphoid ligament and the scaphoid. It moves inward and backward toward the sole, and this is accompanied by the very oblique change in position of the malleoli, which, of course, move with it in this rotation, the inner malleolus backward and the outer malleolus forward. As the foot is supinated, there is a movement downward of the scaphoid over the head of the astragalus as well as a movement inward.

An important question may now be brought up in connection with this discussion. During the execution of flexion and extension in a seemingly simple ginglymoid diarthrosis like the ankle joint, what is the function of the fibula? Does it possess much elasticity; does it move, and if so, how and where?

We shall mention the opinions of several investigators, beginning with Humphry,[3] who stated:

> It is not enough to say that the socket of the leg bones is shaped in conformity with this configuration of the articular surface of the astragalus. For, if that had been all, and if the fibula had, like the inner malleolus, formed a part of the tibia so that the socket had been hollowed out of the solid bone and had maintained an unvarying size, it could not have been adapted to the astragalus in the different positions of the limb. It would have either been too large when the joint was *extended* or too small when it was *bent*. But the outer malleolus, being a little movable, permits a slight alternate widening and narrowing of the socket in flexion and extension; so that freedom of movement is combined with the maintenance of an exact coaptation of the articular surfaces. This yielding of the outer malleolus in a lateral direction, under the pressure of the articular surface of the astragalus during flexion, and its recoil in extension depend not so much upon a yielding of the ligaments that bind it to the tibia as upon the elasticity of the bone itself. Hence a careful examination will show that during flexion, when the malleolus is pressed outward, the shaft of the fibula is, at its narrowest part, just above the ankle, bent a little inwards; and vice versa, when the joint is extended, the shaft recoils to its former distance from the tibia.

Ashhurst[5] stated that Nancrede called Humphry's theory "preposterous and untrue." We cannot find any references about that remark. We believe that these are Ashhurst's own words. In the first place, Nancrede was not aware of the work and teaching by Miles and Humphry some twenty years before him. Nancrede[6] merely answered an attack on him for plagiarism by Dr. Randolph Winslow. Dr. Winslow pointed out to him that all this was known and taught by others. However, Nancrede stated that a little reflection would demonstrate the mechanical impossibility of Humphry's view about the yielding of the external malleolus in a lateral direction during flexion and its recoil in extension.

Nancrede,[7] in another article, went on to explain his views, for a part of which he justly claimed originality.

> . . . all the ligamentous fibers pursue an *oblique course from the tibia downward to the fibula,* and that the capsule of the superior tibio-fibular joint is a loose one.
>
> The diagram [fig. 5] will show the course pursued by the fibers . . . the apposed rough surfaces of the inferior tibio-fibular joint are connected by a short, felt-like collection of fibrous tissue—i. e., the inferior interosseous ligament.
>
> . . . the ligaments must be perfectly inextensible and inelastic to perform their functions properly.
>
> A little reflection will demonstrate that, in walking, the momen. the foot is placed upon the ground the body still tends to go forward from its own impetus, and there is a marked tendency for the leg bones to slip forward upon the dorsum of the foot. This is not theory, but a demonstrable fact. Some provision against this must be made. If the immunity from displacement had to depend on the posterior ligament of the ankle-joint, it would have to be enormously strong. But let it never be so strong, unless it were *tight* it would not prevent luxation. If, however, it were tense in all positions where this forward displacement was liable to occur, it *would render flexion utterly impossible.* What, then, *is* the arrangement found? Simply that the astragalus is wedge-shaped, with its base in front, so that the more the leg bones tend to slip forward the tighter the articular surfaces are pressed together. This also is not theory, but a simple mechanical fact. The shape of the bony surface—excluding the muscles, which, as is too commonly overlooked, are often the most important ligaments of a joint—is absolutely the only obstacle worth mentioning to forward displacement of the leg bones. . . .

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5. Ashhurst, A. P. C., and Bromer, R.: Classification and Mechanism of Fractures of the Leg Bones Involving the Ankle, Arch. Surg. **4**:50-129 (Jan.) 1922.

6. Nancrede, C. B.: An Answer to Dr. Randolph Winslow's "Reply" to Dr. Nancrede's Paper upon the Tibio-Fibular and Ankle Joint, Maryland M. J. **7**: 76-78, 1880.

7. Nancrede, C. B.: Some New Observations upon the Anatomy and Functions of the Ankle and Tibio-Fibular Joints, Philadelphia M. Times **10**:316-318 (March 27) 1880.

This shape, however, of the astragalus and its socket, if the latter were rigid, would completely arrest flexion, as the broad anterior end, already firmly embraced by the malleolar arch, could not be made to pass backward into the still narrower portion of the socket, as is actually the case in flexion. . .

How, then, is an *adaptable* socket provided? Simply by having *two* bones in the leg, *one of which is movable*, the other fixed. By examining the diagrams it will be seen that the tibia and fibula can be compared to the two halves of a parallel ruler, and the ligamentous fibers to the two brass arms of the same instrument. Both the ligament and the brass arms are inextensible, but any wedge-like object insinuated between the two halves will push up the movable half and widen the space between them.

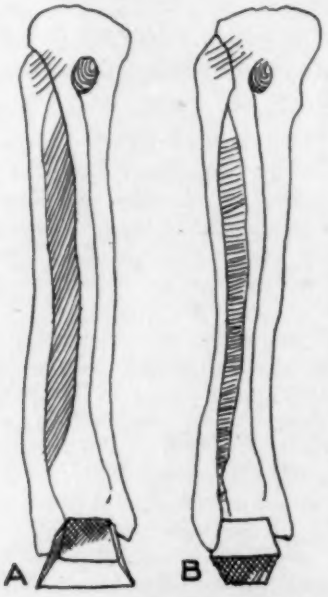

Fig. 5.—Direction of the fibers of the lower part of the interosseous membrane in extension (*A*) and flexion (*B*) of the foot.

Just so in the ankle-joint. In extreme extension [fig. 7] the narrow part of the astragalus is carried forward to that part of the socket which before accommodated the wide portion of that bone; and yet there is complete apposition of the bony surfaces, because the movable bone—i. e., the fibula—glides down. Again, in flexion the wide anterior portion of the astragalus is pressed between the narrower portion of the socket, which is widened by the fibula gliding *upward*. This upward gliding approximates the attachment and origin of the ligamentous fibers just enough to permit the two malleoli to be sprung apart sufficiently to admit the base of the astragaloid wedge. From the mode of attachment of the middle band of the external lateral ankle ligament—viz., in front and above the apex of the internal malleolus [he meant external malleolus]—this structure is tense in every position of the joint, and especially in extension winds around the malleolus, thus pulling it down and narrowing the socket in the extended position when such a condition of the malleolar arch is demanded.

From the foregoing statement it is apparent that Nancrede should claim originality for his views about the gliding upward and downward of the fibula.

NOTE.—In our brief communication on the structure and function of the ankle joint, the universally accepted views have been put forth as a matter of simplicity. These views are shared to a great extent by the original researches of von Meyer, Langer, Henke, Heuter, Meissner, Goodsir and others. Mr. W. Arbuthnot Lane, however, making an independent and exhaustive examination of the ankle joint in 1888, offered views on this subject, some of which differ materially from those mentioned in our review. The latter author called attention to the following facts:

(*a*) One must examine the astragalus in the recent state and not as a dry bone; one will then observe a "ligamentous facet" or "triangular area" as being cut off from the posterior and outer part of its upper surface; it is nonarticular; during flexion the posterior ligament, together with the posterior inferior tibiofibular and the posterior portion of the external lateral ligament, rests and plays on the triangular area.

(*b*) Also, during flexion of the ankle, the ligaments which are chiefly engaged in preventing the separation of the malleoli by the wedge-shaped internal articular surface of the astragalus are: the anterior inferior tibiofibular ligament, the posterior fasciculus of the external lateral ligament and the back part of the deltoid ligament. The interosseous membrane, the posterior inferior tibiofibular ligament and the inferior interosseous ligament take but a secondary share in this work.

(*c*) In complete extension of the ankle joint the concavity on the projection on the back of the astragalus comes into contact and articulates with the corresponding little articular surface on the tibia and with the adjacent portion of the posterior inferior tibiofibular ligament; the impact of these two opposing surfaces limits the movement of extension. In this position the only other articular surfaces in contact with each other are the outer articular surface of the talus with the corresponding facet on the outer malleolus.

(*d*) The transverse ligament is but a portion of the posterior ligament of the ankle joint. This posterior ligament is a distinct and important structure. It is attached externally to the fibula in the interval between the attachments of the posterior inferior tibiofibular ligament and the posterior fasciculus of the external lateral ligament. It consists of radiating fibers which cover in the ankle joint posteriorly. The upper margin of this ligament is practically continuous with the posterior inferior tibiofibular ligament and its lower limit with the posterior fasciculus of the external lateral ligament.

(*e*) The posterior fasciculus of the external lateral ligament limits and opposes movements both of complete flexion and of complete extension of the ankle joint, for the reason that its fibers occupy a horizontal plane and the interval between its points of attachment is least where the joint occupies a position midway between complete flexion and extension. Any deviation from this posture renders the fibers oblique.

(*f*) The same author maintained, therefore, that in any degree of flexion or extension of the ankle the head of the astragalus cannot be displaced inward owing to the strain exerted on it in an outward and backward direction by the anterior fasciculus of the external lateral ligament. It cannot be displaced outward on account of the strain

Fig. 6.—*A*, descent of the fibula in plantar flexion; *B*, ascent of the fibula in dorsiflexion.

exerted on it by the anterior portion of the deltoid ligament in a backward and inward direction.

REVIEW OF THE LITERATURE

In 1756 Sir Percival Pott suffered a compound fracture of both bones of the lower part of the leg, which resulted not only in his survival but in the repair of the fracture and later in 1768 in a description of "Pott's fracture." We refer the reader to this interesting and sparkling treatise in a compilation by Sir James Earle, "The Chirurgical Work of Sir Percival Pott, with Observations." [8]

We were not only regaled by this description but by the good judgment shown by Sir Percival when he refused to be transported from

8. Pott, Percival: The Chirurgical Works of Percival Pott, Philadelphia, J. Webster, 1819, pp. 246-252.

the site of the accident until the leg had been immobilized, a principle in treatment of fractures which is neglected by the modern surgeon and the attendant of the police ambulance.

Pott, in his treatise, pointed out the power which the peroneus muscles acquire in consequence of the loss of support occasioned by fracture of the fibula and the resulting eversion and elevation of the foot.

Preceding and following Pott up to the time of Sir Astley Cooper [9] and Dupuytren [10] were several interesting writers, among whom we may mention Petit [11] (1723), Bromfield [12] (1773), Pouteau [13] (1783), Castella [14] (1808) and Bell [15] (1809).

Cooper [9] (1830-1840) seems to have had an appreciation of the various dislocations, including posterior displacement, which occurs in posterior marginal fracture.

Dupuytren [10] (1830-1840), in a masterful treatise on "Fractures of the Fibula" in which he reported 207 cases with 5 deaths, specially pointed out the ligament tears, the result and the fact that dislocation of the foot at the ankle joint does not occur without fracture.

We now come to Maisonneuve [16] (1840), who described lateral dislocation of the foot with high fibular fracture, now known as the Maisonneuve fracture, and presented an interesting discussion on the mechanism of injuries to the ankle. He was first to point out the importance of the tibiofibular diastasis which we are emphazing in this paper.

In 1879 Tillaux [17] discussed fractures of the ankle, and the so-called "third fragment" was introduced.

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9. Cooper, A. P.: A Treatise on Dislocations and Fractures of the Joints, edited by B. B. Cooper, Philadelphia, Blanchard & Lea, 1851, pp. 246-298.

10. Dupuytren, Gillaume: On the Injuries and Diseases of Bones, translated and edited by F. le Gros Clark, London, New Sydenham Society, 1847, pp. 234-315.

11. Petit, Jean-Louis: Traité des os: Dans lequel on a représenté les appareils et les machines qui conviennent à leur guérison, Paris, C.-E. Hochereau, 1723.

12. Bromfield, W.: Chirurgical Observation and Cases, London, T. Cadell, 1773.

13. Pouteau, Claude: Oeuvres posthumes, Paris, P.-D. Pierres, 1783.

14. Castella, M.: Essai sur les fractures du péroné, Landshut, J. Thomann, 1808.

15. Bell, Charles: A System of Operative Surgery, Founded on the Basis of Anatomy, ed. 2, London, Longman [and others], 1814, pp. 363-365.

16. Maisonneuve, J. G.: Recherches sur la fracture du péroné, Arch. gén. de méd. **1**:165-187 and 433-473, 1840.

17. Tillaux, Paul: Traité d'anatomie topographique avec applications à la chirurgie, Paris, Asselin & Houzeau, 1879.

Hoenigschmied [18] in 1877 made some exceedingly interesting studies, 125 in all, on cadavers to determine the mechanism of fracture of the ankle.

Bondet in 1899 and Destot [19] in 1911 introduced physiologic classifications, adopted later by Quenu [20] and Tanton, both of whom used these classifications and added to theories in mechanism.

The mechanism of Pott's fracture was one of the favorite discussions in the clinics of Dr. John B. Murphy.[21] One of us remembers with what emphasis Dr. Murphy described the mechanism. He also recognized the importance of diastasis but denied the possibility of Pott's fracture occurring by inversion of the foot.

The advent of the x-rays has greatly enhanced our knowledge of the many combinations of fragments, of the dislocations and especially of the posterior marginal fragment and the arthritic changes which follow these fractures.

Fig. 7.—*A*, compression fracture; *B*, bimalleolar fracture; *C*, simple Pott's fracture without fracture of the internal malleolus, and *D*, simple Pott's fracture with an oblique fracture of the fibula above the malleolus and the internal malleolus—the common type.

Among the outstanding American writers are Kellogg Speed,[22] who published a report based on a study of 208 cases of Pott's fracture from from the Cook County Hospital, and Ashhurst and Bromer,[5] who

18. Hoenigschmied, J.: Experimente über die Zerreissungen der Bänder im Sprunggelenk, Deutsche Ztschr. f. Chir. **8**:239-260, 1877.

19. Destot, Etienne: Fractures de la région malléollaire, in Traumatismes du pied et rayons X, 1911, pp. 75-134.

20. Quenu, E.: Plaies de pied et du cou-de pied par projectiles de guerre, Paris, F. Alcan, 1918, pp. 185-190.

21. Murphy, J. B.: Pott's Fracture, Surg. Clin. **1**:451, 1912; Ancient Pott's Fracture: Operative Reduction; Nailing of Malleoli, ibid. **5**:349, 1916.

22. Speed, Kellogg: A Discussion of Pott's Fracture with Complications, Based on a Series of Two Hundred Eight Cases, Surg., Gynec. & Obst. **19**:873-882, 1914.

reported 300 cases of fractures of the ankle, giving, perhaps, the most detailed classification with an interesting study of the literature.

The works of Cotton and Berg,[23] especially on posterior marginal fractures and on a classification according to dislocation, are important landmarks in the development of this subject.

We are also much interested in the fact that Bardenheuer advocated traction in the treatment twenty years ago, a fact which is now generally accepted by the German surgeons, especially Felsenreich [24] and L. Böhler, in the more serious types of fractures of the ankle.

Other interesting contributions have been made by Stimson, Stevens,[25] Shands,[26] Delbet, Robert,[27] Hubmann [28] and Pels-Leusden.

MECHANISM OF FRACTURES OF THE ANKLE

In considering the mechanism of the ankle joint, one notices that the column transmitting the weight of the body from the thigh to the foot consists of two bones, which are so united as to form a solid medium, the fibula gliding to a slight extent upward and downward during dorsiflexion and plantar flexion, respectively, allowing no lateral motion. The base of the column is the foot, but the ankle joint is not placed in the center of the weight-bearing arch of the foot. If a vertical line is dropped from the center of the base of the femur, it falls on the inner part of the astragalus, which is itself placed at the inner and posterior part of the foot. This accounts for the greater power of the adductor or supinator muscles. This line again divides the foot as regards its anterioposterior axis into two unequal portions, nearly three-quarters being in front of and one-fourth behind the center of gravity. It is well known, as pointed out by Osgood, that in the uninjured and healthy limb the adductor or supinator muscles exceed the pronator muscles in strength in the proportion of 5 : 4. But as soon as fracture of one of the bones of the lower part of the leg is produced, the ratio does

23. Cotton, F. J., and Berg, R.: Ankle Fractures: New Classification and New Class, New England J. Med. **201**:753-760 (Oct. 17) 1929.

24. Felsenreich, Fritz: Untersuchungen über die Pathologie des sogenannten Volkmannschen Dreiecks neben Richtlinien moderner Behandlung schwerer Luxationsfrakturen des oberen Sprunggelenks, Arch. f. orthop. u. Unfall-Chir. **29**:491-529, 1931.

25. Stevens, James H.: Compression Leverage Fractures of Ankle Joint, Surg., Gynec. & Obst. **38**:234-252, 1924.

26. Shands, A. R.: Fracture-Dislocations of the Ankle: Analysis of Series of One Hundred Nine Cases, Internat. J. Med. & Surg. **42**:238-244, 1929.

27. Robert, Leslie: Treatment of Ankle and Leg Fractures by the "Delbet" Ambulatory Plaster Splint, Brit. J. Surg. **15**:414-429, 1928.

28. Hubmann, Paul: Ueber die Frakturen des obern Sprunggelenks mit besonderer Berücksichtigung der hinteren Luxationsfraktur und ihrer Behandlung, Beitr. z. klin. Chir. **147**:417-433, 1929.

not hold any more. The long and short peroneus muscles, assisted by some of the muscles lying in front of the ankle (the extensor digitorum longus and peroneus tertius), overcome the power of the adductor or supinator muscles and therefore evert the foot and help to produce a lateral dislocation.

For this reason we must forget previous conceptions that all Pott's fractures are produced by turning the foot outward and that turning the foot inward produces, when fracture occurs, always a medial dislocation.

Clinical experience is of no assistance, since most patients cannot remember whether they turned the foot outward or inward.

For this reason any classification on an etiologic basis is untenable; nor does the dislocation reveal the mechanism.

Some authors explain the mechanism entirely along mechanical lines, having in mind the weight-bearing axis, various levers, stress

Fig. 8.—*A*, Pott's fracture with posterior marginal and posterior dislocation (a Cotton fracture); *B*, Pott's fracture with marked posterior dislocation but no posterior marginal fragment, and *C*, Pott's fracture with anterior chip (a Tillaux fragment).

and strain. Under "Anatomy and Physiology of the Ankle Joint" we have shown that the movement of the foot is not in a direct antero-posterior plane but in a plane inclined outward and obliquely, owing to the outward inclination of the toes, to the slight twisting of the tibial shaft and to the posterior position of the external malleolus. This, plus other factors, such as the varying equinus position of the foot (females), genu valgum or varum, the weight of the body, the type of the shoe, the grade of the terrain and other extrinsic forces, all bring forth various factors in the mechanism of production, and, after all, interest us in the mechanism of this fracture more from an anatomic standpoint.

Most writers in describing Pott's, or pronation, fracture have held the view that one of two lesions occur primarily. Stimson, Bonnet and Tillaux stated that the first lesion is the tear of the internal lateral

ligament or the internal malleolus, which allows the tibia to move laterally and later to act as a fulcrum in fracturing the fibula. Murphy, Speed, Ashhurst and Maisonneuve stated that the astragalus in eversion of the foot acts as a fulcrum, first fracturing the fibula, and that the anterior inferior tibiofibular and the internal lateral ligament tear later in Pott's fracture.[25]

Maisonneuve in 1840 was the first to appreciate the rôle played by the inferior tibiofibular ligaments in the production of fractures of the ankle. Other writers have referred to the diastasis and the disability resulting therefrom.

Examination of leverage injuries of the ankle joint, whether sprain or Pott's fracture, invariably shows local tenderness slightly medial and inferior to the external malleolus, pointing to a lesion of the anterior inferior tibiofibular ligament (Aitken, 1934).

The collateral ligaments are the strongest ligaments of the ankle joint. The inferior tibiofibular ligaments, although resistant to force, are subject to constant strain in any position of the foot. This strain is accentuated by the up and down movement of the distal end of the fibula during flexion and extension. This fact, brought out in our anatomic discussion, has been previously overlooked to a great extent.

Measurements made after fracture-dislocations of the ankle joint show commonly a widening in the mortise due to diastasis of the tibiofibular articulation. Reference to our "Analysis of Data" shows this condition present grossly in 40 per cent of the roentgenograms. It is difficult, unless comparative roentgenograms are made, to determine a little diastasis.

The foregoing anatomic and clinical facts lead us to believe that the tear in the anterior inferior tibiofibular ligament with subsequent diastasis is not only a constant lesion in leverage injuries of the ankle joint, including sprains, Pott's fracture and other types of fracture, but that it is the primary lesion.

We know of no permanent way of proving our observations but feel that our views are fairly well founded on an anatomicopathologic basis, whereas the opinions of previous writers are only theories visualized on mechanical grounds.

In more severe violence the posterior inferior tibiofibular ligament and even the interosseous ligament may be torn, causing more marked diastasis.

After a tear in the tibiofibular ligament, it acts as a fulcrum, the degree of tear determining the site of fracture in the fibula. With a tear in the interosseous ligament, the fracture is high on the fibula, as described by Maisonneuve.

The tear in the anterior inferior tibiofibular ligament is followed by a tear in the internal lateral ligament, and this, together with the

up and down movement of the fibula, allows a rotary movement of the astragalus. This accounts for the large percentage of oblique fractures (153 in 300 roentgenograms).

As before stated, Pott's fracture can occur with both supination or pronation of the foot at the time of accident. When pronation does not result after supination, there is a medial dislocation with a vertical or an oblique fracture in the tibia or in the internal malleolus.

A bimalleolar fracture is usually caused by supination or pronation but may be also caused by a fall forward or backward, with the foot either in plantar flexion or in dorsiflexion. The latter mechanism also accounts for a solitary anterior or posterior marginal fracture, in some of which we find a tear in the anterior or posterior tibiofibular ligament with diastasis.

Fig. 9.—*A*, Pott's fracture with a posterior chip (a Tillaux fragment)—low oblique fracture of the fibula; *B*, Maisonneuve's type of Pott's fracture—a high fracture of the fibula, and *C*, simple Pott's fracture with fracture of the internal malleolus—low subperiosteal fracture in the external malleolus.

A marginal fracture usually occurs as a complication of pronation, supination or bimalleolar fracture. The posterior lip is more often involved because of its greater posterior declination. A posterior marginal fracture is more commonly seen in females than males, which leads us to believe that the equinus position of the foot allows greater rotation and backward displacement of the foot.

CLASSIFICATION

A study of 378 roentgenograms of fractured ankles makes us wonder why a classification should be made at all. It seems more natural to report each individual case according to the roentgenographic picture.

On the other hand, some classification which is simple must be used for teaching purposes. Our conception of these injuries does not permit a classification merely on the type of dislocation, since there are tears in the ligament and various combinations of fragments, nor can we consider one on an etiologic basis such as suggested in the excellent monograph by Ashhurst and Bromer.[5]

Regardless of any objection to placing a colleague's name in the classification, one must agree that for years English-speaking people have called the pronation fracture of the ankle joint Pott's fracture. There may be no Pott's fracture, but for the sake of precedent and usage from now on we shall classify all fractures of the lower part of the fibula with lateral dislocation of the foot as Pott's fracture; the reverse, as supination fracture. When there is no dislocation, one has simple or bimalleolar fracture. A compression fracture refers to upward dislocation of the astragalus with comminution of the lower end of the tibia and the fibula.

Should there be a small anterior or posterior lip (a Tillaux fragment) or an anterior or posterior marginal fragment (figs. 9 *B* and *C* and 10 *A*), this condition is considered as a complication. Solitary marginal fracture is rare. Thus we may refer to Pott's fracture with a posterior fragment or a bimalleolar fracture with an anterior Tillaux fragment.

This classification takes into consideration that lesions of the ankle consist of tears in the ligament, dislocations and fractures and quickly suggests to the student both the pathologic process and the treatment required.

TREATMENT OF INJURIES TO THE ANKLE

The main objects in treating injuries of the ankle joint are as follows: (1) to reduce the dislocation, (2) to reduce the fracture, (3) to reduce the tibiofibular diastasis, (4) to maintain a reduction until ligamentous and bony repair has been obtained, (5) to protect the vascular system during the repair and (6) to restore function.

As a temporary measure, in all cases of simple injuries of the ankle we apply a posterior molded splint lined with sheet wadding. This is often done at home to protect the injury and make the trip to the x-ray laboratory or hospital more convenient to the patient. After the patient is hospitalized all compound fractures are surgically cleaned by débridement. No internal suturing is done, and the skin is closed without drainage. Fractures are immediately reduced, and a posterior molded splint is applied. If the wound is extensive and is so placed that the cast might produce pressure, the fracture-dislocation

is treated by means of a Kirschner wire or a Steinmann pin through the os calcis, extension being best obtained with the knee bent on a Braun or Böhler splint.

It is important to ascertain whether the fracture-dislocation has occurred in the usual manner or whether there has been additional direct trauma, such as the limb's being run over by a car wheel, or any other form of contusion, since in such accidents the patient must be informed

Fig. 10.—*A*, epiphysial separation with a posterior marginal fracture running into the epiphyseal line; *B*, supination fracture, and *C*, simple fracture of the external malleolus.

of the likelihood of blebs, gangrene or sloughs, lest he later blame the surgeon's splint.

In simple fractures without dislocation or displacement an anesthetic may not be necessary since the limb can be immobilized with the usual posterior molded splint. If, however, there is considerable tenderness over the anterior inferior tibiofibular ligament or should the roentgenogram show a distinct diastasis, we even then use a local or general anesthetic in order to apply the redresseur.

Reduction.—This is done as soon as diagnosis is made by means of a roentgenogram. Should there be a swelling, the limb is elevated for twenty-four hours, and effleurage is used to reduce the edema.

The reduction should be done with the patient under an anesthetic, either local or general, preferably ether or ethylene. In all cases of Pott's fracture reduction is performed with the leg flexed at right angles, dorsiflexion and adduction of the heel being used, and for supination fracture-dislocations the reverse of this procedure is

Fig. 11.—Pott's fracture with posterior marginal fracture, showing marked diastasis, suggesting also involvement of interosseous ligament.

employed—with either type of fracture, the foot being held in mid-position.

All posterior dislocations with posterior marginal fragments are reduced with cautious dorsiflexion (see maintenance of reduction).

The internal malleolus, when fractured and displaced, is pushed upward with the palm of the hand.

Bimalleolar fracture is treated in midposition with right angle dorsiflexion.

It is the purpose of this paper to add one additional procedure in the reduction of Pott's fracture; that is to reduce the diastasis by

means of a redresseur to the lower part of the tibia and fibula above the malleoli. The instrument is applied for from three to five minutes, the compression being removed just before the unpadded posterior molded splint of plaster is applied. Not alone is the diastasis overcome, but a better mortise and position of fragments are effected in a bimalleolar fracture. Neglect to reduce the diastasis results in abnormal lateral motion, pes valgus, shortening of the tendo Achillis, faulty weight bearing and later arthritic change.

Fig. 12.—Simple Pott's fracture. The fibula is fractured at a still higher level.

When diastasis is marked and second roentgenograms still show separation, we apply extension by the Kirschner wire, which puts the collateral ligaments on stretch, thereby bringing the tibia and the fibula together. We here caution against overextension (fig. 14).

A common error is to put a supination fracture with medial dislocation in adduction. This only increases the dislocation.

When a posterior marginal fragment complicates fracture, caution should be used not to put the foot in too much dorsiflexion.

A compression fracture is treated as a routine with Kirschner wire through the os calcis. The reduction of dislocation can be obtained by adjusting the bow of the Kirschner apparatus. The redresseur is usually used later for this type of fracture because of the greater tendency to edema and blebs.

Maintenance of Reduction.—It is easy to reduce Pott's fracture even when complicated by a marginal fragment, but is is difficult to

Fig. 13.—Pott's fracture with anterior and posterior marginal fractures.

maintain the reduction, because the diastasis predisposes to redislocation of the astragalus. Formerly, many poor results could be attributed to the circular cast padded with so much cotton that the reductions were lost in the shrinkage of the plaster.

The ordinary type of Pott's fracture can be best immobilized in a posterior molded splint without padding. This splint is applied immediately after the redresseur has been removed and extends from the middle of the thigh to beyond the toes. A walking iron can be applied several days later in cases of the more simple types of fracture by

means of circular plaster above the malleolus and above the knee. Our statistics show that the average immobilization is about five weeks in a case of simple Pott's fracture and much longer when there is a posterior marginal fragment. In the latter cases one may not be able to maintain reduction in the ordinary plaster splint, and under such circumstances we advise using a pin or a Kirschner wire extension on a Böhler splint for five weeks. We advocate that extension be used more

Fig. 14.—Overextension and deformity caused by improper traction.

often in cases of the severe types of fractures of the ankle to reduce the diastasis, to prevent redislocation and to keep the posterior fragment pulled down.

Roentgenograms are made immediately after the reduction, and in cases of anterior or posterior marginal fragments they are made every seven days until union is assured.

In many cases a boot made of a paste of zinc oxide [29] is desirable during the next few weeks to support the circulation. Weight

29. The composition of this zinc oxide paste by weight is as follows: 1 part of chemically pure zinc oxide, 2 parts of good gelatin, 3 parts of water and 4 parts of chemically pure glycerin.

bearing varies with the amount of swelling and union. The average weight bearing in simple Pott's fracture is eight weeks. We advise against weight bearing in a case of Cotton fracture for a period of from twelve to fourteen weeks.

Restoration of Function.—Passive motion is entirely omitted from our treatment. Active motion can be obtained even with a boot of a paste of zinc oxide. When the boot is not used, we find our best results in restoring function to be derived from the use of baking, Swedish massage and hot and cold foot baths.

The only additional treatment which we employ is the application of the redresseur in reducing tibiofibular diastasis, which is present in all injuries to the ankle, and to advocate a greater use of extension (traction) to prevent disabilities.

SUMMARY

In our report, supplemented by a morphologic and physiologic study and a clinical study of the pathologic picture of fractures of the ankle, we have emphasized the following points:

1. The primary lesion in leverage fractures of the ankle joint is the tear in the anterior inferior tibiofibial ligament, followed by a certain amount of diastasis.

2. The height of the fibular fracture depends on the degree of diastasis plus the gliding of the fibula in dorsiflexion and plantar flexion (already described).

3. The diastasis in the inferior tibiofibular articulation is the cause of much disability, faulty weight bearing and arthritic changes and should be prevented at the time of injury by applying a redresseur or even traction with a Kirschner wire at the time of reduction and immobilization.

4. All abduction fractures of the ankle joint should be called Pott's fracture. We have given a simple classification, including all other types of fracture and their complications.

RETROPERITONEAL TERATOMA

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AND
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The literature on the pathologic structure of the teratoma is in a most unsatisfactory state. On a recent occasion three pathologists were questioned as to the elements necessarily present in a tumor to admit it to classification as a teratoma. Each presented different criteria. The literature reveals a similar divergence of opinion, and the confusion is evidenced further by the number of theories that have been advanced by authors to explain the origin of such a tumor. To enter into a discussion of these subjects is beyond the scope of this paper, but the studies presented here strongly suggest that a teratoma arises as a misplaced blastomere. The more nearly totipotent the cell, the more differentiated will be the tumor when it grows.

Recognizing fully the objections to this theory, we believe that it still remains the most logical explanation of parasitic monsters and teratomas. By following this reasoning, teratomas may be subdivided into two types: the true teratoma and the teratoid tumor. The former, containing the analog of one or more organs, is derived from a more nearly totipotent blastomere than the latter, which is unable to produce any formed organ, even though it, too, contains representatives of all the embryonal elements. The transition between these artificial classes is so gradual that the classification accorded any borderline tumor depends on the pathologist. In reviewing the literature listed in the bibliography, we have attempted to ascertain from the description of the tumor whether or not formed organs were present, and our review has revealed thirty-six cases of retroperitoneal teratoma. The data in these cases, with the exception of those in the cases presented by Karvonen and Cahill, reports of which were not available, are recorded in the accompanying table. In addition we desire to present a new case which we have observed.

REPORT OF A CASE

P. S., a 29 year old man, was admitted to the surgical service of Dr. I. S. Ravdin in the Hospital of the University of Pennsylvania on Sept. 9, 1935, with a chief complaint of pain in the right side of the abdomen. He stated that his

From the Surgical Clinic and the Laboratory of Surgical Pathology, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research.

Data on Cases of Retroperitoneal Teratoma and Teratoid Tumor Reported in the Literature up to 1936

Author	Sex	Age*	Location of Tumor	Size	Manner of Obtaining Specimen	Result of Operation	Formed Organs Present	Symptoms
Baljasov	F	21	.....	..	Operation	Death	....	.....
Bauer	M	14	Left	M	Operation	.....	Yes	.....
Brouha	F	26	Left	L	Operation	Death	No	.....
Dickinson	F	2	Right	S	Autopsy	.....	No	Mass
Durante and David	..	Neonatal	Lumbar	M	Autopsy	.....	Yes	.....
Feldmann	M	20	R. U. Q.	S	Autopsy	.....	No†	Mass
Gordon	F	50	.....	L	Operation	Recovery	No	"Pressure symptoms"
Gross	F	26	R. U. Q.	S	Operation	Recovery	Yes	Mass
Gude	F	9	L. U. Q.	M	Operation	Death	Yes	Mass
Hosmer	F	8 mo.	Right	L	Autopsy	.....	Yes	Mass
Irna	F	9 mo.	Left	M	Operation	Death	....	.....
Johnson and Lawrence	M	33 mo.	Left	S	Exploration	Death 8 mo. later	Yes	Mass
Kaneko	M	10 mo.	L. U. Q.	M	Autopsy	.....	Yes	Mass; cachexia
Kolb	F	7 wk.	Left	S	Autopsy	.....	Yes	Mass; cachexia
Kostitch	M	22	L. U. Q.	L	Operation	Death	Yes	Mass; pain
Kuznetsoff	M	..	Left	L	Exploration	Death	No	Mass; cachexia; constipation
Landiver and Iparraguirre	M	45	L. U. Q.	M	Operation	Recovery	Yes	Pain
Lexer	F	11	L. U. Q.	..	Operation (twice)	Recovery	No	Fever; pain; mass
Lightwood	..	9 wk.	R. U. Q.	S	Autopsy	.....	No	.....
Marchand	F	35	L. U. Q.	S	Operation	Death	No	Mass
Maydl	F	..	.....	..	Operation	.....	Yes	.....
Meckel	..	..	L. U. Q.	..	Autopsy	.....	No	.....
Nicholson C. M.	M	25	R. U. Q.	S	Exploration	Death	Yes	Mass; vomiting; pain
Nicholson, G. W. P.	F	4 mo.	L. U. Q.	S	Autopsy	.....	Yes	.....
Pilliet	F	24	Lower	L	Biopsy	Death	....	Mass
Portugal	F	17	L. U. Q.	S	Operation	Death	Yes	Mass; vomiting; pain
Roux	F	25	Umbilicus	L	Autopsy	.....	No	Mass; uremia
Ruge	M	27	Left	L	Operation	.....	Yes	.....
Seki	M	22 mo.	Left	M	Autopsy	.....	Yes	.....
Shonholzer	M	2	Epigastrium	M	Autopsy	.....	Yes	Mass; pain
Terasako	M	3 mo.	R. U. Q.	S	Operation	Death	No	Mass
Tillaux	F	22	L. U. Q.	M	Operation	Death	No	Rapid growth
Tsuda	M	17 mo.	Left	L	Operation	Death	....	.....
Usandizaga and Mayor	F	28	L. L. Q.	S	Operation	Recovery	No	Pain
Watanabe	M	23	L. U. Q.	S	Autopsy	.....	....	Mass

* Figures indicate years when not otherwise specified.
† Malignant.

health had been perfect until ten days before admission. Then, for the first time, he had noticed a dull pain in the right lower quadrant of the abdomen. This pain caused him to stop his regular work in a hosiery mill. A local physician examined him "thoroughly" and ordered him to bed. At no time did he have nausea, emesis or pyrexia. After two days of rest in bed the pain disappeared completely. On September 5, following the advice of his physician, the patient took a bottle of solution of magnesium citrate to relieve obstipation of six days' duration. This was effective, and after the passage there was noted for the first time a large nontender lump in the right upper quadrant of the abdomen. The mass persisted without change until his admission on September 9. Two days before, while walking, the patient was suddenly seized with knifelike pains in the right upper quadrant of the abdomen. These were excruciating for from five to six hours but after that gradually lessened in intensity until the time of his arrival at the hospital. Still there was no nausea, vomiting or fever.

His past medical history was essentially irrelevant, except that he had noted increasing constipation for the preceding two years. His family and social histories were not enlightening.

On physical examination, the patient was found to be well developed and to present no essential abnormality, save for the condition in his abdomen. In this region there was slight generalized tenderness, but no muscular spasm. In the right upper quadrant, nearer the umbilicus than the costal margin, a firm, smooth mass was felt, which on palpation seemed to be about the size of a lemon. It was well circumscribed and apparently did not extend toward the right costal margin. It was fixed, though it moved slightly with respiration, and was tender only to firm pressure. No other masses or organs were palpable.

Laboratory studies of significance showed a leukocyte count of 17,400 and a slightly accelerated sedimentation time. A roentgenogram taken after an enema of barium sulfate revealed the transverse colon displaced downward by a mass located in the right upper quadrant, which mass lay superior and posterior to the transverse colon but had no connection with it.

After two days' hospitalization a laparotomy was performed by Dr. I. S. Ravdin on September 11. Through an upper right rectus incision, the tumor was found to be lying retroperitoneally just below the liver, on top of the vena cava and lateral to the descending portion of the duodenum. Across its lateral surface ran the right ureter, and across the medial surface, the superior mesenteric vessels. It was covered by the transverse mesocolon, and when this had been divided the mass was found to be well encapsulated. The pseudocapsule or peritoneum was incised, and the tumor was carefully shelled out, with little bleeding. The posterior pole was firmly adherent to the vena cava. The raw surface was peritonized, and the abdomen was closed without drainage.

The patient's course after operation was uneventful. The incision was completely healed at the time of his discharge, on the sixteenth postoperative day. He returned two months later. At that time he felt entirely well, had gained weight and was completely relieved of his constipation. The wound was well healed and showed no evidence of weakness. No recurrent mass could be palpated. A series of high voltage roentgen treatments was given at that time. It was divided so that 50 roentgens was delivered through each of four portals covering the entire abdomen and the lower part of the thorax, and a second portion, consisting of 3,200 roentgens, was directed to the tumor bed.

Six months after his discharge the patient was readmitted to the hospital, because of a different complaint (headache). The opportunity was taken to study him at this time. Physical examination, a urogram and roentgen examina-

tion, after a barium enema, revealed no abnormalities in the retroperitoneal area. He had no symptoms referable to this region. The testicles were normal in size, shape and position.

He returned to the hospital in July 1936, with a painful swelling in the right side of his scrotum. This had developed rapidly, following an injury two weeks before. Examination revealed that the lesion was not traumatic or due to infection but was a neoplastic enlargement of the right testicle. The testicle was somewhat larger than a hen's egg and was firm, smooth and slightly tender and surrounded by a small amount of fluid. The patient's general condition was good, and he had lost no weight. General physical examination gave negative results. Orchidectomy was performed, and on microscopic examination typical teratomatous tissue was found, which we believe was the result of metastasis from his original tumor.

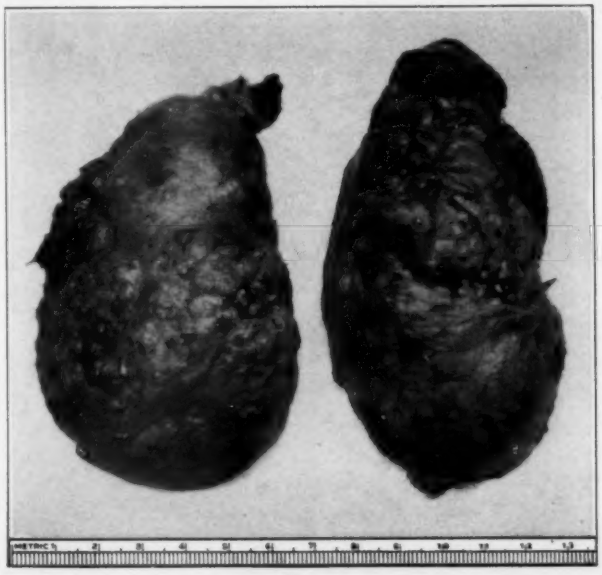

Fig. 1.—Outer view of the tumor, showing the nodular appearance. The site of attachment is at the top of the picture.

His fourth admission was only ten days later, and at this time he complained of a constant, dull, dragging pain in the right lower quadrant of the abdomen. There were no associated urinary or gastro-intestinal symptoms other than some increase in constipation.

Examination revealed a large firm, fixed mass just below the scar of the original operation and a smaller lesion farther down in the right lower quadrant. These had not been palpated at the time of the previous admission. Roentgen studies of chest, loins, spine and pelvis gave negative results, but the right iliopsoas muscle was partially obscured, apparently by the overlying tumor. These lesions seemed to be extensions of the original lesion. They were hard and fixed. We did not believe that they could be removed by operation. Roentgen therapy was begun immediately, and over a period of three weeks the patient received a total of 4,450 roentgens through six portals, covering the chest,

abdomen and pelvis. During this time his pain was completely relieved, and the palpable masses decreased considerably in size. He was told to return for further irradiation after six weeks' rest.

Pathologic Report.—Grossly the tumor was the size and shape of a large pear. It measured 10 by 6 by 5 cm. and weighed 155 Gm. The surface was covered with a glistening capsule, save for an area 3 cm. in diameter, which was the apparent site of attachment. Its surface was irregular and nodular (fig. 1). These whitish yellow nodules measured from 1 mm. to 1.25 cm. in diameter. To palpation they felt firmer than the supporting tissues. On section the tumor was found to be made up of myriads of small cysts (fig. 2), the great majority of which were filled with a sebaceous material. There was a second group of apparently thinner-walled cysts which contained a clear serous fluid. A third, less common class was observed, which contained both clear serous fluid and sebaceous material.

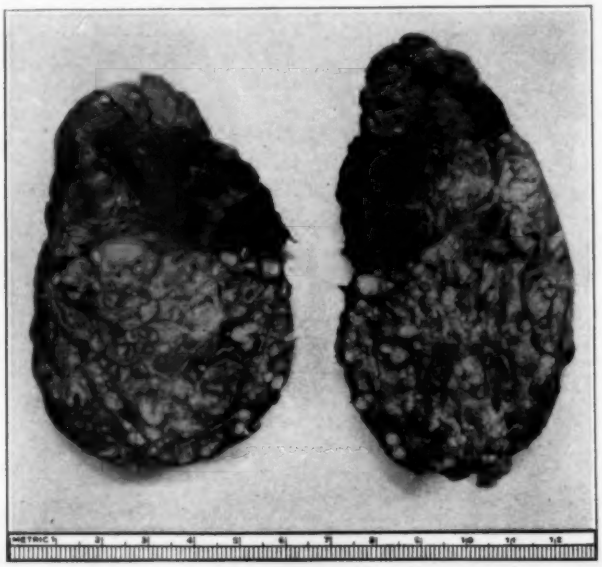

Fig. 2.—Inner view of the tumor, showing cystic structure. The areas of hemorrhage may be seen plainly.

The last two types of cyst were found, in the main, near the posterior attachment of the tumor. In the same area were several fairly well organized hemorrhages, the largest of which measured 3 by 3 by 1.5 cm. No formed organs were seen grossly.

Microscopically the tumor showed wide structural variations. Predominating were structures of mesoblastic origin. Among these, in order of frequency, were encountered spindle cells and connective tissue, moderate-sized, localized areas of angiomatous tissue, small areas of adipose tissue and one small plaque of cartilage. There was no evidence of the presence of muscle or bone.

Tissue of hypoblastic origin was least frequently seen. Several areas showed columnar epithelium bearing goblet cells. These were arranged in a manner resembling the glandular formation of the large intestine. The apparent secretion of these cells took the eosin stain. Occasional cysts were lined with epithelium of

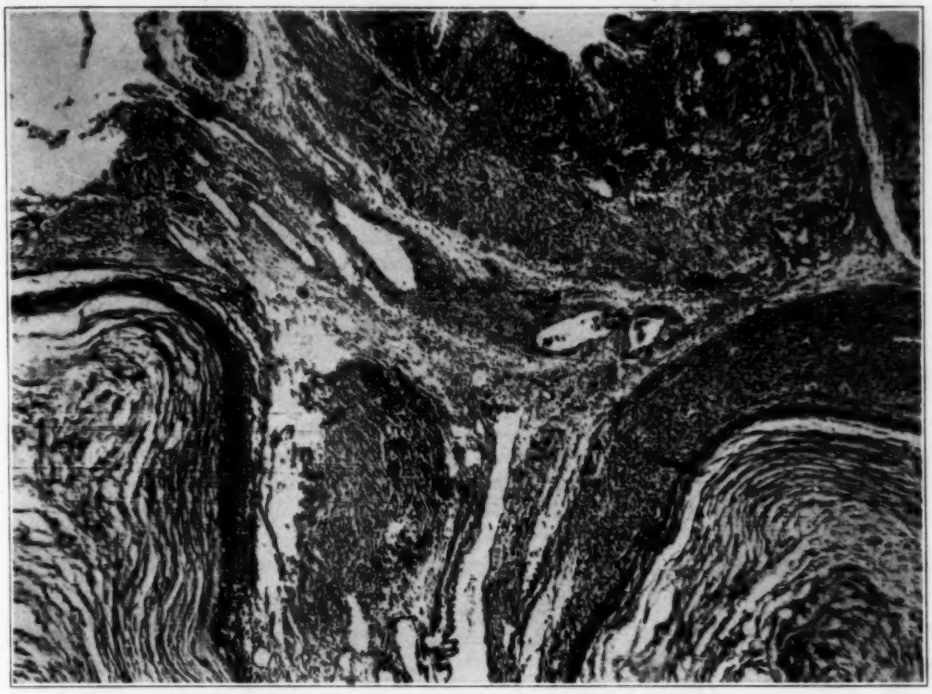

Fig. 3.—Photomicrograph showing three of the many cysts found in the tumor. The upper one is lined with goblet cells, and the lower two are lined with endothelial cells and filled with a colloid substance.

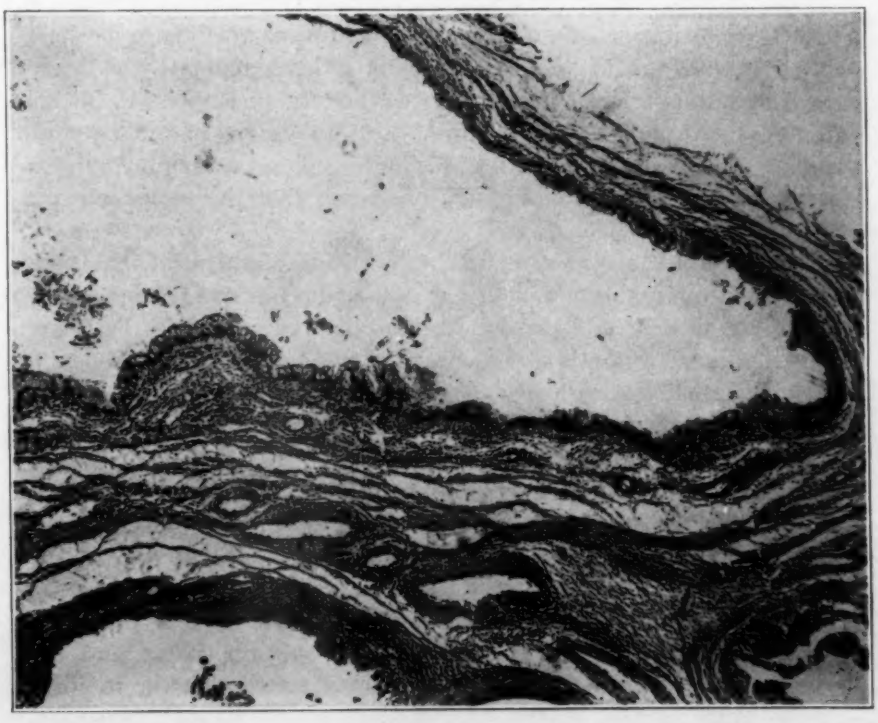

Fig. 4.—Photomicrograph showing a cyst lined with three different kinds of epithelium.

a pure columnar variety and others with a pure transitional type. In the latter class several papillary projections were observed. No cilia were demonstrated.

Epiblastic tissue was manifested by epidermoid cysts. These did not have hair, sweat glands or papillae, and it was impossible, therefore, to identify them as true skin. In one section there was observed what appeared to be a rudimentary hair follicle which contained no hair. By the use of silver stains, we discovered no evidence of neuro-epithelium.

There were some points of special interest in the microscopic examination: Several cysts were present which contained stratified, columnar and transitional epithelium (fig. 3). In some instances the cysts were empty. In others they contained what appeared to be desquamated epithelium. Still others had an eosin-stained secretion.

There were two hemorrhagic areas, one of which showed a more advanced degree of organization than the other. In the older of these great numbers of macrophages were observed to be carrying blood pigment. In the other the hemorrhage issued into a previously angiomatous region. There was some necrosis of the tissue adjacent to the hemorrhagic areas, and in these places were seen many old polymorphonuclear leukocytes, with a surrounding wall of lymphocytic infiltration.

There was no evidence of malignancy in any of the sections studied.

PATHOLOGIC STRUCTURE

The tumor under discussion contained elements representative of all the primary embryonal layers, but since it contained no formed organs it was necessary to classify it as a teratoid tumor. Both Lexer and Portugal stated that true teratomas are less common than teratoids. Kuznetsoff maintained that in the retroperitoneal area the opposite is true. An analysis of the cases presented here supports this view: Nearly two thirds of the growths were true teratomas. G. W. Nicholson has shown that several studies seem to report inaccurately the presence of formed organs. An epithelium-lined cyst containing an occasional goblet cell does not justify concluding that the tumor contains large intestine.

Structurally the tumor under study was not unusual. The great number and approximate equality in size of the cysts were noteworthy. Cysts containing three kinds of epithelium have been recorded by Lexer, Pilliet, Dickinson and others. The majority of tumors contain bone, but a roentgenogram of the tumor described here failed to reveal its presence. The area of cartilage was unusually small. No cholesterol crystals were detected by fresh smears.

The fact that one area of hemorrhage appeared to be further organized than the other gives rise to the thought that there may have been recurrent hemorrhages.

The size of the tumor under discussion was about the same as that of the growth in the case of Gross, which was the smallest previously recorded. That tumor also was located in the right upper quadrant, and the patient recovered after operation. Lexer stated that the majority

of the tumors were located in the left upper quadrant, and, indeed, we were able to find only five previously reported that were located in the right upper quadrant.

CLINICAL SURVEY

A review of the cases studied shows some points of clinical interest. While there is no information available, it is probable that in few of the cases was a diagnosis made before operation or autopsy.

A tumor of this type is found usually before the patient reaches the age of 30. There were but three cases reported in persons past that age. Forty per cent of the patients were in the first decade, and 34 per cent, in the third. Distribution was nearly even between the sexes, fifteen being males and eighteen females.

An abdominal mass was the chief complaint in most instances. Pain was the next most frequent symptom, ranging in severity from a vague backache to the acute pain seen in the case here described and probably related to the hemorrhage found in the tumor bed. Vomiting and constipation were noted occasionally. These were due, in all probability, to external pressure. Fever was mentioned only once.

Rapid growth of the tumor was reported by Tillaux and was taken to indicate malignant change. Gradual loss of weight was the rule, and cachexia was seen in the terminal stages.

Physical examination invariably showed a tumor. The size ranged from that of a lemon to that of an adult head; the growth was usually located in the left upper quadrant, and generally was fixed. Edema of the extremities was recorded in several cases, and with a small tumor this might easily give a clue to the location of the lesion.

There are a few studies that might be of diagnostic value: A flat roentgenogram of the abdomen might reveal pieces of bone in the tumor. A roentgenogram taken after a barium enema would give valuable information as to the relative position of the tumor. One taken after the retroperitoneal injection of air, after the method suggested by Cahill, might aid further in localization. Urograms and pyelograms would help to rule out renal lesions, although they might show evidence of distortion due to external pressure. It is noteworthy that although such a tumor is in close juxtaposition to the kidneys, renal symptoms (except in the case reported by Roux) have been absent.

The chief differential diagnosis must be made from hypernephroma and retroperitoneal sarcoma. The more rapid evolution of the mass, the early onset of cachexia and the early metastasis point to the more malignant lesions. Often a hypernephroma gives rise to early renal symptoms and causes defects in the roentgenogram of the urinary tract. The presence of a febrile reaction is common in cases of sarcoma.

There are but two methods of treating these lesions. The first is surgical exploration and the removal of the tumor, either in whole or in part. In the cases here reviewed, twenty-three of the patients were operated on, of whom only seven survived—an operative mortality of 70 per cent. Of the seven who recovered, one died eight months later. Only a biopsy specimen had been removed from this patient at operation. In the remaining six patients the tumor was entirely extirpated, and as far as can be stated from the information available, there were no recurrences or further symptoms. Most of the deaths followed attempts at removal of a very large lesion. The cause of death in the majority of cases was hemorrhage and shock. Some of the patients might have been saved had modern methods of intravenous infusion and transfusion been available.

The other possible method of treating such a tumor is by interstitial irradiation. There is little information available on the subject, although it is well known that the tumor is highly radioresistant. The method might have definite application, however, in those instances in which the tumor appears to have undergone malignant degeneration. In a tumor which has been incompletely removed or from which a biopsy specimen has been taken, there is danger of seeding. From the malignant behavior of such seedings it must be deduced that they have taken in their growth a more anaplastic character than the cells from which they arose, in which case they should be more radiosensitive. We believe that all incompletely removed tumors and those from which biopsy specimens have been taken should have adequate roentgen therapy.

SUMMARY

The literature on retroperitoneal teratoma is reviewed.

A new case of retroperitoneal teratoid tumor is presented. The tumor was extirpated, and the patient was well six months after operation.

The diagnosis and treatment of lesions are discussed.

Dr. I. S. Ravdin granted us permission to discuss his case in this paper; Drs. A. E. Bothe and Charles C. Norris reviewed the slides, and Mr. Kitamura, a student at the university, supplied the translations of Japanese articles.

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TREATMENT OF COMPOUND FRACTURES

RESULTS IN ONE HUNDRED CASES OF COMPOUND FRACTURES OF THE TIBIA

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The result of any surgical procedure depends almost as much on the surgeon and his application of it as it does on the merits of the procedure itself. In no field is this more true than in the treatment of compound fractures. Here each fracture presents an individual problem, no two being exactly alike in any of the many particulars which affect the method and result of treatment. Even if one cannot or should not adopt a standard routine procedure for all fractures, it does seem that the treatment of so common and serious an injury should be more standardized than it is today. There is varied and conflicting counsel in textbooks and journals, and even in the large surgical services there is usually no standardized method of treatment. The results obtained by any of the various methods are not satisfactory. Cotton said: "Judging from what I see of end results, I fear that the problem of handling compound injuries needs constant attention and constant emphasis." In this situation it behooves every one periodically to review and critically and honestly evaluate the end-results of whatever method or methods he is using. I have tried to do this for the fractures treated in the first surgical division at the Bellevue Hospital during the past ten years. Because they are the most numerous and offer the most favorable opportunity for comparing different methods, this review has been limited to compound fractures of the tibia. During the past ten years 100 such fractures have been treated on which the records are complete as far as immediate results are concerned. Final results as determined by a follow-up study of more than one year were obtainable in 72 cases. These fractures were treated in a general surgical service by various methods by numerous surgeons and house officers. While this has many disadvantages, it does offer an opportunity to compare different methods.

The results have been bad. There have been numerous infections, several amputations and a few deaths. Part of this may be blamed fairly on the type of patient coming to a large city hospital. Many are addicted to the use of alcohol, many have eczema or ulceration of the legs and nearly all have dirty skin and clothing. However, most of the blame for the bad results must rest squarely on the surgeon. That these

results are not peculiar to this service is evident from a study of the literature and by results seen elsewhere. Hey Groves said: "The results of treatment are extremely bad."

The chief problem in treating these injuries is the prevention of serious infection. There are many factors involved which do not lend themselves to statistical study. However, by analyzing a large number of cases of this type of fracture, one should be able to evaluate to some extent the importance of certain factors. In 23 of the cases at the Bellevue Hospital some degree of infection developed, varying from a mild subcutaneous cellulitis, or a persistent sinus, to violent sepsis.

The most important factor of all, as far as infection is concerned, is promptness of treatment. This is only partly under the control of the surgeon, but its importance should be strongly and repeatedly emphasized, so that there will be no unnecessary delay, such as results from transferring the patient from one hospital to another, etc. Of the patients entering the Bellevue Hospital more than two hours after the accident, infection developed in 50 per cent, whereas of those brought in less than two hours after the fracture occurred, infection developed in only 20 per cent. Admission to the hospital from one to two hours after the accident does not mean prompt treatment. Ideally the patient should be on the operating table within an hour after the accident. This factor is so important that I believe it is a mistake to lay too much stress on the treatment of shock and of the patient's general condition, as is done in most textbooks and medical schools. Débridement, reduction and immobilization of a fracture need not be shocking procedures and can well be carried out coincidentally with the treatment of shock. In fact, I think that it is a part of this treatment. Certainly a patient will recover from shock more readily with the fracture reduced and securely immobilized than he will in uncomfortable, inefficient temporary splints. The time element is so important that débridement should be carried out without delay while the patient is receiving infusion or transfusion and other measures to combat shock.

Every one agrees that débridement and mechanical cleansing of the large wounds communicating with a fracture should be done when the patient is received reasonably early. However, there is a difference of opinion as to whether anything is gained by débridement of the small puncture wounds made from within outward by spicules of bone or by the sharp edges of larger fragments. These wounds are small and innocent looking, the fragments have slipped back into more or less good position, and it is a temptation to apply a little iodine, cover the wound and treat the injury as a simple fracture. Estes advocates this simple course, and as evidence that others besides my co-workers and me do not always practice what they preach, Leland reported débridement of only 12 of 22 wounds. However, the size of the wound bears little relation to the damage to the parts beneath, and bits of dirt or

clothing may have been pulled into even a small opening. Therefore, we believe there should be no compromise. Débridement and mechanical cleansing should be done of all wounds communicating with a fracture, no matter how small. Cotton, Foster, Speed and Wilson agree with this. We had 27 cases of fracture which were seen early in which the wound was less than ½ inch (1.3 cm.) in length. Débridement was done in 7, and infection developed in only 1; débridement was not done in 20 cases, and infection developed in 5. Thus the incidence of infection was cut almost in half by débridement. It is reasonable to suppose that the smaller and cleaner wounds were the ones not subjected to débridement, making the decrease in the rate of infection even more striking.

Many writers speak of the danger of further contamination of the wound while scrubbing, owing to soap and dirt being carried into the wound. Some advise covering the wound and not attempting to scrub the edges. Leaving the most important part of the operative field untouched seems entirely illogical to us, and we believe that the danger can be obviated by scrubbing the wound under a constant stream of water. The direction of flow is always away from the wound, and there is but little chance of carrying dirt into it. The process should be just as thorough and conscientious as the cleaning of the surgeon's hands. Asepsis is only as strong as the weakest link in the chain, and it is most unreasonable to spend eight or ten minutes by the clock scrubbing and disinfecting the hands, covering them with rubber gloves and then operating in a field that has been carelessly cleaned and painted with some confidence-inspiring antiseptic. The operative field should be scrubbed for at least ten minutes under a constant stream of water, cleaned with alcohol and ether and then painted thoroughly with iodine or some other antiseptic. The edges of the skin and all devitalized tissue should be excised and the wound again irrigated.

After cleansing and débridement, the question arises whether to close the wound, drain it, pack it open or start immediate treatment with a diluted solution of sodium hypochlorite. Cotton, Estes and Stimson advise loose suture of the cleaner wounds, without drainage. Wilson and Cochrane advise suture only in the cases in which treatment is given within twelve hours after injury and in which the surgeon feels absolutely certain that mechanical sterilization has been obtained. Gurd uses the bismuth-iodoform paste treatment popularized during the World War. This is essentially the same as the Orr treatment, as the mild antiseptic value of the bismuth-iodoform paste is of no importance. Foster leaves the wound open and treats immediately with a diluted solution of sodium hypochlorite. Of the cases of fracture at the Bellevue Hospital in which the patient was treated soon after injury, débridement and suture without drainage were done in 34; of these, infection developed in 7, 21 per cent. Twenty-five wounds were left open without drains or packing; of these, 5, or 20 per cent, became infected. Of the

12 packed open, infection developed in 2, or 17 per cent. Thus it is seen that statistically there is little difference between suturing, packing and leaving the wound open. Except for the fractures seen soon after the accident, packing is the safest treatment. Little is lost by packing as the wound heals by granulation before bony union occurs. One important fact is brought out by the 7 cases in which suture and drainage were done; the wound in 3, or 43 per cent, became infected—more than double the incidence by any other method. The rubber tissue drain inserted "because there is oozing" or "to allow the escape of serum" is not only useless but definitely harmful. It acts as a foreign body, increasing the exudation and preventing the tissues from exerting their strong defensive mechanism. All these wounds are contaminated, but if the tissues are given a chance they will overcome what organisms remain after débridement. This is becoming universally recognized as regards the peritoneum, joints and blood stream, and we believe that it holds true of bone and muscle. There should be no compromise, no middle ground. Either the wound should be closed, or it should be left open and packed lightly with gauze treated with petrolatum.

All of our patients were treated either by traction or with plaster splints or casing. Statistically, there is little difference in the incidence of infection, 30 per cent of those treated by traction and 24 per cent of those treated in plaster becoming infected. We believe that when the fragments can be held in good position in plaster, the secure immobilization is a great advantage in decreasing the incidence of infection and delayed union. Three of the 21 patients treated by traction had delayed union, whereas only 1 of the 63 treated in plaster failed to get bony union within six months.

Numerous surgeons have had the temerity to apply internal fixation to these open, potentially infected wounds. According to Wilson and Cochrane, the method has been superseded and should be used only in rare and exceptional cases. Hey Groves is more vehement. He stated: "I say quite deliberately that I regard the plating of an open fracture as a surgical crime." In the face of this, Foster reported results in a large series of fractures from Sherman's clinic which no one else has approached. Of 304 fractures, he plated 146 and not only had no severe infections but had fewer persistent sinuses in the cases in which plating was used than in those in which it was not employed. Recently we plated a few compound fractures with good results, but we believe that the method should be reserved for the exceptional fracture, i. e., the fracture seen soon after injury in which mechanical cleaning is satisfactory and in which reduction cannot be retained by other methods.

We were forced to amputate in 5 cases. In 2 of these primary amputation was done because of nonviability of the foot. One man refused operation on admission to the hospital, and infection developed, necessitating amputation. In a boy of 12 years with extensive avulsion

of the skin and soft parts by a crushing injury, a severe infection developed, and the leg was amputated on the fourth day. Another fracture involving the ankle joint was manipulated in the presence of active infection, which is extremely poor surgical judgment, and a violent flare-up of the infection occurred, necessitating amputation.

In this series of 100 cases there were 8 deaths. Five were due to associated injuries and 1 to pneumonia three weeks after the fracture, so that only 2 deaths may be directly attributed to the injury. In 1 of the fatal cases the wound was closed loosely without drainage, and the fracture was immobilized in plaster splints. In the other débridement and loose suturing were done after the insertion of two soft rubber drains. A posterior molded splint was applied. The wound was infected, and amputation on the seventh day did not save the patient's life. The two surgical errors in this case—partly closing and draining the wound and poor immobilization—undoubtedly contributed to the fatal outcome. A posterior molded plaster splint is an absolutely useless gesture toward immobilization, yet for some queer psychologic reason it is one of the most frequent methods of splinting. The splint always breaks at the knee and ankle because a flat strip of plaster has practically no resistance to bending in the direction of its flat surface; also it is applied over the irregular thick soft parts of the calf rather than over the medial surface where the bone is superficial. In minor fractures, where one strip of plaster is to be relied on it should be applied on the lateral or medial surface, and the lower end passed under the instep and over the dorsum of the foot. Applied in this way it at least has some effect.

CONCLUSIONS

I have nothing new or startling to report in the treatment of these fractures, but a fairly large series of fractures is reported in order to emphasize the seriousness of this injury and the great room for improvement in results obtained here and elsewhere. The mortality, loss of function, period of hospitalization and economic loss are greater than for surgical diseases which receive much more attention and thought.

After reviewing the subject I feel more strongly than ever that this type of fracture presents an urgent surgical emergency. Débridement and thorough cleansing of all wounds that communicate with a fracture should be done no matter how small or clean they seem. The apparently clean wounds that are seen soon after injury in which mechanical cleansing is adequate should be sutured without drainage. Where treatment has been delayed or is not adequate for any reason, the wound should be left wide open and packed lightly with gauze treated with petrolatum. Immobilization in a plaster is superior to traction suspension in that it lowers both the incidence of infection and the incidence of delayed union or nonunion.

A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 210)

BLADDER

Physiology.—Rubritius [52] stated that the hollow muscular organs behave according to the laws which govern all the nonstriated muscles. The peristalsis of the hollow tubiform organs as well as the phases of filling and evacuating of hollow spherical organs can be explained by these principles.

During the phase of retention the wall of the bladder expands by the accumulation of urine, while its resistance remains the same. During this phase the internal pressure of the abdominal cavity is transmitted only partially to the internal pressure of the bladder on account of the tonus, that is, the resistance of the wall of the bladder. The capacity of the bladder is dependent on the tonus of the moment. When the maximal capacity has been reached, the contractive stimulus passes into the most extended muscular zone, that is, into the detrusor muscle.

With the contraction of the detrusor muscle, the sphincter relaxes. The tonus of the sphincter and the tonus of the detrusor muscle are

52. Rubritius, Hans: Die Physiologie der ableitenden Harnwege, Kong. d. internat. Gesellsch. f. Urol. **6**:499-574 (Sept.) 1936.

dependent on each other; therefore, the sphincter remains open until the detrusor muscle has contracted completely, while the closing contraction of the sphincter puts an end to the contraction of the detrusor muscle. If the tonus of the sphincter is abnormally high, the closing contraction begins prematurely, and residual urine remains in the bladder. The presence of residual urine has a compensatory effect, because a bladder holding residual urine can work more economically and stand a higher pressure, so that it may keep up its function in spite of the obstacle to the outflow of urine.

While the bladder is contracting (transporting phase of the bladder), the peristalsis of the upper portion of the urinary tract ceases. The pelvis of the kidney and the ureter remain in a state of tonic extension (phase of retention). In the meantime the orifices of the ureters do not open, and urine flows out of the collecting tubes into the calices and into the pelvis of the kidney. The alternation of the phases of the bladder with those of the upper part of the urinary tract is regulated by reflexes. Any disturbance causes a vesico-ureteral reflux or upward flow.

Recent research has demonstrated that the resorptive efficiency of the mucous membrane of the urinary passages increases with the increasing dilatation of the mucous membrane. Gruber has confirmed the statements of former research workers that a close relation exists between the capillaries and the epithelium of the mucous membranes. This is especially true within the fornix calicis. It is known that the fornix calicis is the most extensible part of the urinary tract. Macroscopic rupture of the mucous membrane of the fornix calicis is of great importance in urinary retention, but there is no reason to look on this rupture as a physiologic phenomenon. If the mucous membrane in the fornix stretches to such an extent that there is utmost thinning of the epithelial cells although rupture has not yet occurred, this mucous membrane becomes permeable.

Urinary passages are, from a physiologic point of view, a closed system, the single morphologic units of which are working hand in hand. The connection of this system with its headquarters, the parenchyma of the kidney, seems to be very ingenious and enables undisturbed cooperation between them. In the urinary passages muscular action is completed by resorptive action. While the physiologic analysis of the former can be considered ideal, new questions are arising with regard to resorptive functions. Their importance from the standpoint of metabolism, the entire body and the connection with the minute collecting system of the kidney with the secretion of this organ are no doubt of great importance for future research.

Calculus.—Hueck [53] in ten years performed 171 operations for stone in the bladder. A previous operation had been performed to remove calculi in 14 of these cases, and in 1 case 2 previous operations had been performed. A single stone is usually found, as was the case at 50 operations on 44 patients. The average interval between surgical intervention and reformation of the stone was four years and eight months; in 1 instance it was less than a year. Because of the frequent adhesions between the peritoneum and the bladder, the author advised operation by the perineal route for recurrent calculus with the patient under sacral anesthesia. Thirteen of the patients were men, and 1 was a woman who had a vesicovaginal fistula. In 3 other cases of stone in women, vaginal fistulas were also present. This led the author to think of catarrh of the bladder as a predisposing factor of formation of calculi.

Of the 171 operations, only 10 were performed on females, whose ages ranged from 7 to 75 years. In Professor Olpp's series of cases of vesical calculi from the same hospital, 4 of the patients were women and 201 were men. Twenty of the author's patients were boys. In a series of 100 recent cases, 9 patients died within one month after the operation. This figure included elderly persons and those in whom complications developed. He had another series of 45 operations without a death.

In the author's opinion there has been no decrease in the number of cases of vesical calculus in recent years. Regarding the cause, he thought that hypothetically the body constitution, the composition of water and vitamin deficiency may play a rôle; ankylostomiasis, malaria and the dysenteries are listed among the predisposing causes. In this connection, Hueck commented on the rarity of cases of stones in Europe at present compared with their frequency in the Middle Ages.

Digby [54] stated that litholapaxy takes much time and patience. The actual procedure for stones over 1 inch (2.5 cm.) in diameter may consume from three quarters of an hour to a couple of hours. This compares unfavorably with the twenty minutes or less required for suprapubic cystostomy, but the extra time involved is well repaid by the benefits to the patient. Open warmed ether administered by a pump is the routine anesthetic. The table is slightly tilted so that the head is lower, and there has not been any difficulty with bronchitis in this class of case. From a theoretical point of view, sacral anesthesia should be ideal, as it should produce anesthesia of the bladder and urethra and

53. Hueck, O.: Beitrag zur Blasensteinerkrankung, Chinese M. J. **50**:833-836 (June) 1936.

54. Digby, K. H.: Observations on Litholapaxy, Chinese M. J. **50**:837-846 (June) 1936.

relaxation of the detrusor fibers. It has been tried in a few cases and has worked out badly. Contrary to physiologic theory, the bladder seems to contract around the stone and interfere with manipulations. Spinal anesthesia is mentioned only to be condemned, at any rate, for the neglected patient with a large stone of long standing and possibly damaged kidneys. Such cases form the bulk of the cases of vesical calculus. Spinal anesthesia lowers the blood pressure, and anuria may follow. Digby stated that he had encountered this condition more than once when he had been called to see a patient in consultation after operation by others. Spinal anesthesia has not been employed for removal of a vesical calculus in his clinic.

Litholapaxy is contraindicated in the following circumstances: 1. When there are signs of renal failure, such as suppression or extreme diminution in excretion of urine or a glazed and dry tongue, or the value for blood urea is more than 50 mg. per hundred cubic centimeters. 2. When the prostate gland is felt to be much enlarged on rectal examination or has been producing symptoms. In this case a suprapubic cystostomy with extraction of calculi should be followed in a week by suprapubic enucleation of the prostate. In these cases there are usually multiple calculi. More than one stone in an old man should always raise the suspicion of enlargement of the prostate gland, as should also the discovery of residual urine. 3. When there is a stricture of the urethra of any marked degree. Although the stricture can be dilated and the litholapaxy proceeded with, the more prudent method is to accompany the dilation with suprapubic cystostomy, unless the stricture is slight. 4. When the stone has caused a penetrating ulcer of the wall of the bladder so that extraperitoneal extravasation of urine has occurred, or a vesicosuprapubic fistula or a vesicorectal fistula has formed. 5. When advanced cystitis is present to such a degree that the urine is foul smelling, brown and ammoniacal and the bladder cannot be distended with fluid. In such cases suprapubic cystostomy is wiser. 6. When the stone is large. This is usually but not always a contraindication for litholapaxy. Very large stones have been crushed by experienced surgeons.

A surgeon should always be prepared to deal with any possible accidents. The posterior part of the urethra or the neck of the bladder may be perforated in passing one of the instruments. The wall of the bladder may be nipped and crushed. Severe crushing of the wall can be avoided by rotating the blades in the initial position before crushing the stone. The blade of the lithotrite used for the male may break or, worse, may bend. In the first case the lithotrite can be withdrawn without the blade. The broken blade has to be removed suprapubically. In the second case, after the bladder has been opened suprapubically, the blades should be protruded as far as possible and

an attempt made to detach the bent blade with a hack saw. If the blades cannot be protruded far enough, the staff must be sawed through with a hack saw and the bent distal part of the lithotrite extracted through the suprapubic wound. The blades may jam on a cystine calculus. A fragment of stone may be overlooked at litholapaxy and become impacted in the urethra before the subsequent cystoscopy.

Kya [55] reported the results of a chemical analysis of vesical calculi in 42 cases. In 16 cases (38.4 per cent of cases analyzed) the stones contained uric acid as the chief constituent; in 18 cases (43.2 per cent of cases analyzed) there were mixed stones containing uric acid, calcium oxalate and calcium phosphate in balanced proportions. He stated that mixed stones are the commonest variety, and next to them are the uric acid stones. Rarely are pure stones of one constituent only found. The result of analysis of this series agrees with the figures of Jones in England, of Newcomb in India and of Thomson in Canton in that stones containing uric acid and urates as the chief constituent form a higher percentage than other stones.

Oxalate stones are seen in children, while uric acid or urate stones are obtained from middle aged or elderly patients.

The visibility of vesical stones of different chemical composition in roentgenograms has been dealt with. Kya had only 1 pure uric acid stone which was translucent to the roentgen rays. All other uric acid stones showed well in the roentgenograms, because they contained a certain proportion of calcium. Pure cystine is invisible in body tissue to detection by roentgenographic examination, but the stone which was 96 per cent cystine, 0.8 per cent calcium and 0.6 per cent phosphate showed distinctly in the roentgenogram. The opacity was probably due to the contained calcium.

Lett [56] stated that during the thirty year period previous to 1934 there were 2,781 patients with stone in the urinary tract admitted to the London Hospital. A study of this series suggests that stone in the urinary tract as a whole is twice as common in the male as in the female. The sex of the patients with stone in the kidney was fairly evenly distributed, as 849 of the patients were males and 719 were females. Of those with stone in the ureter, 353 were males and 179 were females, so that the former outnumbered the latter in the proportion of 2:1. However, when the patients with stone in the bladder were considered, there was a very great preponderance of males, as only 8.2 per cent of the patients were females.

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55. Kya, L. T.: The Composition of Vesical Calculi, Chinese M. J. **50**:797-806 (June) 1936.

56. Lett, Hugh: On Urinary Calculus, with Special Reference to Stone in the Bladder, Brit. J. Urol. **8**:205-232 (Sept.) 1936.

During the last ten years of the period under review there was a considerable increase in the number of patients with urinary stone admitted to the London Hospital, for, including those with stones impacted in the urethra, they numbered 1,085 as against a total of 778 admitted from 1915 to 1924, an increase of nearly 50 per cent. The number with renal calculi rose from 485 to 644; with ureteral calculi, from 130 to 208, and with vesical calculi, from 140 to 212. However, the number of patients with urethral calculi decreased from 23 to 21. Instead of an increase in the number of children with stone, the incidence fell from 69 during the period from 1905 to 1914, to 27 during the last ten years, largely owing to a diminution in the number of patients with stone in the bladder and urethra. It is interesting to find a definite increase during the five years that followed the World War, particularly in the number of patients with stone in the kidney.

Stones were found in the kidney in 1,568 patients, in the ureter in 532 and in the bladder in 608. The total of 2,781 patients in the series is completed by 73 with stone in the urethra. Thus there was a combined total of 2,100 persons with stone in the kidney and ureter as compared with 608 with stone in the bladder.

The urine of 750 consecutive patients with stone in the urinary tract was examined. This group was made up of 487 with stone in the kidney, 140 with stone in the ureter and 123 with stone in the bladder. The reaction of the urine was acid in 72 per cent of all instances in which it was examined. No report was made on the reaction of the urine of 4 of the patients with renal calculus, but that of 347 was acid, that of 41 was neutral and that of 95 was alkaline. Repeated examinations of the urine of a number of patients were made; the reaction of specimens of 103 varied on different occasions, while the first specimen of 67 was acid. Reports were made on the urine of 139 patients with calculus in the ureter; that of 102 gave an acid reaction, that of 10 was neutral and that of 27 was alkaline. Repeated examination of the urine of 29 patients disclosed varying reactions, while the first specimen of 24 was acid. The urine of 88 of the 123 patients with vesical calculus was acid, that of 10 was neutral and that of 25 was alkaline. There were 25 patients whose urine gave different reactions on repeated examinations, and 22 whose first specimen was acid.

Tumor.—Gehrmann [57] stated that prolonged exposure to relatively low concentrations of certain intermediates produced during the manufacture of dyes and classified as aromatic amines is known to have caused the development of tumors of the bladder in certain persons. The carcinogenic compounds already mentioned enter the circulation

57. Gehrmann, G. H.: Papilloma and Carcinoma of the Bladder in Dye Workers, J. A. M. A. **107**:1436-1438 (Oct. 31) 1936.

through three routes: (1) respiratory, (2) cutaneous and (3) gastro-intestinal. It is generally agreed that the most important route of entrance is through the respiratory tract, in the form of dust and fumes. Absorption through the gastro-intestinal tract is probably of the least importance. However, it must be remembered that present knowledge indicates a long period of exposure to low concentrations as an etiologic factor. Therefore, any absorption through the gastro-intestinal tract should be considered as of more or less importance, despite the low solubility of these compounds.

The classic symptoms of tumor of the urinary bladder are hematuria, frequency, urgency, burning and pain. These symptoms as a group occur in Gehrmann's experience only in those cases in which the condition is well advanced. It has also been his experience that cystoscopic examination is the only safe method of early diagnosis. The growths may be single or multiple, papillary or sessile, infiltrating or noninfiltrating, ulcerating or nonulcerating, malignant or benign. In Gehrmann's group of 63 cases of tumor of the urinary bladder, 38 were carcinomas.

The histologic structure of the aniline tumor does not differ from that of tumors of unknown etiology. The aniline tumor occurs in all gradations, from the slowly growing villous papilloma, which may remain latent for many years, to the rapidly growing destructive and anaplastic carcinoma, which produces early and widespread metastasis.

Preventive measures are divided into two groups: plant operative control and medical control. The plant operative measures consist of manufacturing processes that provide complete protection against any exposure to dust or fumes. Every applicant for work in regions in which he will be exposed to aniline, alpha and beta naphthylamine and benzidine should have a cystoscopic examination in addition to a regular complete physical examination. Any disease of the genito-urinary system is a contraindication to employment, as is a family history of cancer and a history of hematuria or venereal disease. No applicant for this type of work should be accepted who is less than 21 or more than 40 years of age. All workers should have a complete physical examination and cystoscopic examination once a year. Every three months there should be a complete urinalysis and, on the appearance of macroscopic or microscopic blood, cystoscopic examination is indicated.

The prognosis is good in cases of benign tumor. However, further growths may occur at any time and may be primarily benign or malignant. The prognosis in cases of malignant aniline tumor of the bladder in general is not favorable. Simon expressed the belief that this type of growth is biologically different, runs a slower course and responds better to therapeutic procedures.

Dart [58] reported a study of the cell types and the methods of grading of the cases in the Carcinoma Registry of the American Urological Association. Since the opening of the registry in May 1927, more than 1,400 cases have been reviewed. Follow-up reports have been obtained each year on all but 77 cases. One thousand, two hundred and twenty-four of the 1,400 cases were used as the basis of this report.

With few modifications, the present criteria for grading tumors of the bladder used in the registry office are the same as those adopted by the original registry committee in 1927. These criteria are based on a combination of clinical factors and the histopathologic appearance of the specimen. For the purpose of these studies this has been designated as the registry grade. As a check on the efficiency of the registry grade, the registrar chose other criteria based solely on the histopathologic appearance of the tumor. This is referred to as the histologic grade. The underlying principles used in establishing the histologic grade are much the same as those which have been followed more or less consistently by all workers since Broders first announced his method.

The final grade and status of the 1,224 epithelial tumors of the urinary bladder were as follows: The registry grading (clinical data and cellular character) revealed 46 papillomas and 65 carcinomas of grade 1, 347 carcinomas of grade 2, 584 carcinomas of grade 3 and 182 carcinomas of grade 4, making a total of 1,224. The histologic grading (cellular character) revealed 101 papillomas and 200 carcinomas of grade 1, 266 carcinomas of grade 2, 459 carcinomas of grade 3 and 198 carcinomas of grade 4, making a total of 1,224.

Based on all of the facts found, it is believed that the present registry grade may be simplified, to advantage, as follows:

Grade 1. Papillary carcinoma. This type includes all papillary tumors in which there is no clinical evidence of infiltration and in which no obvious infiltration of the pedicle or the wall of the bladder can be demonstrated on histopathologic examination, and most of the cells are typical in appearance and arrangement.

Grade 2. (*a*) Papillary and infiltrating carcinoma. Obviously this type includes infiltrating papillary tumors and carcinomas in which the papillary structure is recognizable but most of the cells are atypical in appearance and arrangement. (*b*) Infiltrating carcinoma. This type includes the nonpapillary squamous cell carcinomas in which the cells are fairly uniform in size and type or have a tendency to form keratohyalin and epithelial pearls.

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58. Dart, R. O.: Grading of Epithelial Tumors of the Urinary Bladder: A Study of the Cell Types and the Methods of Grading of the Cases in the Carcinoma Registry of the American Urological Association, J. Urol. **36**:651-668 (Dec.) 1936.

Grade 3. Nonpapillary infiltrating carcinoma. This classification refers to the very anaplastic infiltrating carcinomas. Practically all of the cells are atypical in appearance, and there is very slight or no differentiation.

Although definite conclusions cannot be made concerning the efficiency of grading of vesical tumors until more growths have been checked for a longer period, these studies indicate that it is impracticable to attempt the segregation of tumors of the bladder into definite groups corresponding to their cell types. For all practical purposes, epithelial tumors of the bladder may be classified as papillary, papillary and infiltrating, and infiltrating. Carcinoma of the bladder cannot be graded on the basis of cell differentiation alone. The mortality for the more differentiated types, such as acanthoma, is practically the same as that for the less differentiated squamous cell tumors. The most practical method of grading is based on a combination of physical and histopathologic observations.

Colston and Leadbetter [59] studied 98 cases of extensively infiltrating tumor of the bladder in which necropsy was performed at the Johns Hopkins Hospital; they attempted to correlate the history, methods of treatment and postmortem observations. The growths were exclusively epithelial tumors, with the exception of 1 sarcoma. Metastasis occurred in 56.1 per cent, and in 10 cases the tumor extended through the wall of the bladder without producing metastasis. Tables are given on each grouping and on the duration of symptoms compared with metastasis and extension, organs involved by metastasis, the pathway of metastasis, the comparison of treatment with occurrence of metastasis and the cause of death in operative cases. The importance of ureteral obstruction with resulting infection and destruction of renal tissue either from direct invasion of the tumor or from sclerosis of the ureteral wall due to scar tissue has been emphasized. A particular study of the microscopic structure of the tumors was undertaken to determine if they could be classed according to the cellular structure and architecture of the tumor as a whole. A tentative classification has been made, consisting in order of frequency of occurrence of (1) papillary carcinoma, (2) transitional cell carcinoma, (3) squamous carcinoma and (4) undifferentiated carcinoma. All of the tumors studied, with the exception of a few in the papillary group, were graded 3 or 4 according to Broders' classification. The papillary carcinomas revealed the smallest incidence of metastasis and the undifferentiated carcinomas the greatest, with the incidence in the squamous and epithelial groups lying between. The undifferentiated group is charac-

59. Colston, J. A. C., and Leadbetter, W. F.: Infiltrating Carcinoma of the Bladder, J. Urol. **36**:669-689 (Dec.) 1936.

terized by extensive and rapid metastasis. The squamous epithelial tumors had a tendency to extend first to the regional lymph nodes, perhaps later involving the liver, lungs or bones, while the other two types of tumors in many instances showed distant metastasis without involvement of the lymph nodes.

As in all series of cases, various types of treatment had been used. It was impossible to state definitely the effects of treatment in the various groups, but the author's impression was that the undifferentiated type and the papillary type responded best to radium and high voltage roentgen therapy, as evidenced by the degree of destruction of the original tumor. The local response of these exceedingly malignant tumors to radium and high voltage roentgen therapy, particularly when more modern methods of treatment are applied, is extremely encouraging, and it is hoped that still better results may be obtained. Radical surgical procedures, including total cystectomy, should be reserved for those growths which have proved resistant to a thorough course of high voltage roentgen therapy and radium therapy.

Barringer [60] stated that the best statistics on carcinoma of the bladder indicate only between 25 and 30 per cent five year cures. This leaves a residue of 70 or 75 per cent of cases in which the patient succumbs to the disease. This means that one should not be satisfied with the present day methods of cure, and this is the reason new operative and irradiation devices are constantly cropping up.

When these cases are considered individually, total cystectomy comes first. Barringer stated that if the operation is performed, suprapubic implantation of the ureters is preferable to the implantation into the intestines, because it is less dangerous. There has been a distinct flare-up in extending the use of external irradiation to the treatment of carcinoma of the bladder. Pfahler has reported a few cures, but his pathologic reports are too inadequate to evaluate these. The statistics of operative removal are impressive. They indicate that the operative removal of carcinoma of the bladder has a definite place in the control of this disease. Its scope appears to Barringer to be limited. It does not seem to be applicable to tumors which involve the trigon too much. His impression is that more urologists in America are controlling vesical tumors by radium implantation than by any other method. Radium with all its faults, and they are many, seems to be able to cure many tumors. Barringer's own trend is definitely away from the suprapubic implantation toward cystoscopic implantation. Further progress in the treatment of difficult infiltrating tumors is probably along lines which combine interstitial irradiation with external irradiation.

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60. Barringer, B. S., in discussion on Colston and Leadbetter,[59] pp. 684-685.

Beer [61] stated that for papillary and infiltrating carcinoma partial cystectomy after electrocoagulation of the surface of the tumor, with or without ureteral transplantation into the bladder, or total cystectomy with implantation of the ureters into the skin or the sigmoid colon are undoubtedly the procedures of choice, and any one who is treating patients suffering from tumors of the bladder should be able to carry out these various procedures. Only by experience will the mortality of the operations in the latter group be diminished. The mortality at present is undoubtedly high for these surgical procedures, not only because the patients are old, as a rule, but usually because they have been neglected for a long time before they come to operation, have more or less damage to the upper part of the urinary tract and perhaps are suffering from local or distant metastasis.

In Beer's recent monograph on tumors of the bladder, a review of the later cases, plus those in his original report, confirmed his original conclusion presented at the International Congress at Brussels in 1927, and his results as far as five year cures are concerned are considerably better than those published by the Carcinoma Registry of the American Urological Association.

For instance, of 88 persons with papillary and infiltrating carcinoma of the bladder treated prior to 1930, 15 died. Of the 73 patients discharged from the hospital, 65 could be controlled. If one subtracts the 8 who were lost from observation and the 15 who died as a result of the operation or causes associated with the operation, 65 remain on whose cases one may base the efficacy of a radical surgical procedure, that is, partial resection with or without transplantation of the ureter. In this group of cases in which radical excision was done there were 24 five year cures, or 37 per cent, which is about twice that reported by Ferguson, based on the Washington Registry.

Moreover, in going over a series of cases in which total cystectomy was performed, the tumor having involved the trigon, both ureters and the neck of the bladder, it was found that in the cases in which operation was performed before 1930 there were 57 per cent permanent cures, which is by far the highest percentage, according to Beer, that could be obtained by any method of surgical approach, and is a most encouraging outlook for the future.

Beer stated that the outstanding conclusions one must draw from Dr. Ferguson's report are (1) that vesical tumors are very serious as a group, (2) that as yet there is no uniformity as to the proper method of treatment and (3) that the more radical the therapy the better is the chance of a permanent cure for the patient.

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61. Beer, Edwin, in discussion on Colston and Leadbetter,[59] pp. 687-688.

In view of the fact that implantation of seeds of radon through the cystostomy wound has given five year cures in only 8.8 per cent of cases, whereas partial cystectomy of the bladder has given five year cures in 18.5 per cent, it must be evident that those who rely entirely on the use of radium are not giving the patient with vesical tumor the care he deserves. As has been repeatedly emphasized, every urologist should be able to treat vesical tumors by innumerable methods. For the simpler small tumors and papillomas and occasionally for papillary carcinomas, transurethral treatment with a high frequency current is surely the method of choice, though in the latter group radium seeds introduced transurethrally may be necessary to eradicate the disease.

Bothe [62] stated that a tumor of the bladder is occasionally well advanced before the patient is studied. In some cases the tumor is in a location that involves considerable risk for surgical removal, or it gives evidence of extensive infiltration. In such cases roentgen therapy should be of great assistance. In the papillary carcinoma the regression established by roentgen therapy facilitates subsequent interstitial irradiation. Irradiation has been used before electrocoagulation for the benign papilloma. It is generally agreed that many benign papillomas have been permanently destroyed by electrocoagulation alone. It is also a fact that follow-up examinations on patients with benign papilloma frequently reveal recurrence. It seems within the realm of possibility that preparatory high voltage roentgen therapy may reduce the incidence of this recurrence.

Higgins reported 5 cases of neoplasm which was primary in and confined to a diverticulum of the bladder in a series of 221 cases of tumor of the bladder which were seen at the Cleveland Clinic. Primary carcinoma of the urinary bladder frequently extends into and involves a diverticulum of the bladder, but a primary neoplasm in a diverticulum is a rather infrequent finding.

In the majority of cases diverticulum of the bladder may be diagnosed readily on cystoscopic and roentgenographic examinations. When blood can be seen spurting from the orifice of the diverticulum, the presence of a neoplasm should be suspected. In 2 cases, after thorough lavage of the diverticulum, persistent filling defects were noted on 2 successive examinations, and preoperative diagnoses were made which were verified at the time of operation. In 1 case the tumor was visualized at cystoscopic examination.

Total resection of the diverticulum containing the tumor is the rational treatment. Whether the intravesical or the extravesical technic is utilized depends on the preference of the surgeon. In this series the

62. Bothe, A. E.: Roentgen Therapy in the Treatment of Bladder Tumors, J. Urol. **36**:643-650 (Dec.) 1936.

extravesical technic was used, and the diverticulum was excised completely with a portion of the bladder in the region of the orifice of the diverticulum. In 2 cases in which the ureters were contained in the wall of the diverticulum it was deemed advisable to divide and ligate the ureters and not attempt to reimplant them into the bladder. Although fulguration of the tumor has been employed, radical operation seems preferable.

In the 5 cases reported by Higgins,[63] 1 patient with papilloma of the bladder died of a cerebral embolism seventeen months after leaving the hospital, but the papilloma had not recurred up to that time. One patient with carcinoma in a diverticulum died suddenly of pulmonary embolism on the twenty-first postoperative day. One patient with carcinoma in a diverticulum lived one year and six months without recurrence. Another patient died of an unknown cause two years after removal of a diverticulum containing a papilloma. The fifth patient is living without recurrence six months after operation.

Diverticulum.—Babics [64] stated that 80 of 117 patients with a diverticulum of the bladder observed at von Illyés' clinic had some marked obstruction to the urinary outflow. Thirty-three were operated on. Stones were found in the diverticulum in 8, cancer in 4 and papilloma in 1. Five patients died after operation. The operative procedure has to be adapted to every patient. When the ureter ends in the diverticulum, it should be transplanted. This was done in 6 instances. Sometimes the kidney is so badly infected that it is better to remove it. Von Illyés when necessary performs a prostatectomy and diverticulectomy as a one stage procedure and has never noticed any disadvantage therefrom. One of these patients died from pneumonia after operation.

Cord Bladder.—Gill [65] gave a brief discussion of neurogenic dysfunction of the bladder with particular reference to cord bladder or that type of dysfunction of the bladder produced by disease of the spinal cord. Two cases of marked vesical paralysis are reported in patients whose only diseases were mild arteriosclerosis and severe diabetes mellitus of long standing. It is believed that the paralysis of the bladder was due either directly or indirectly to diabetes and its effect on the spinal cord, and the reasons for this belief are given. A close cooperation between the urologist, internist and neuropathologist is urged in the study of these extraordinary and unusual cases.

63. Higgins, C. C.: Neoplasms Primary in Diverticula of Urinary Bladder: Report of Five Cases, Am. J. Surg. **33**:78-84 (July) 1936.

64. Babics, Antal: Ueber Blasendivertikel, Ztschr. f. urol. Chir. u. Gynäk. **42**:395-410, 1936.

65. Gill, R. D.: The Diabetic (Cord) Bladder, J. Urol. **36**:730-739 (Dec.) 1936.

Munro [66] stated that for purposes of diagnosis, prognosis and treatment cord bladder resulting from all types of injury to the spinal cord should be divided into four distinct groups.

These may be measured cystometrically against the activity of the normal bladder in terms of initial and sustained tonus, the presence and periodicity of emptying contractions, the absolute amount of residual urine expressed in terms of percentage of fill, the storage capacity of the bladder and the reflex and voluntary sphincteric activity.

With these criteria, cord bladders may be classified as atonic, autonomous, hypertonic and normal.

The only permissible end-result of any cord bladder that is due to injury of the spinal cord is either an uninhibited cord bladder in cases of transection of the spinal cord above the sacral segments, an autonomous cord bladder in cases of destructive lesions of the sacral segments or cauda equina or a normal cord bladder in cases of all other types of injury to the spinal cord.

All types of cord bladder are amenable to treatment by tidal drainage, provided the apparatus is adjusted to suit the type of bladder. Except for complications due to misuse of the apparatus, tidal drainage as a method of treatment of cord bladder of any type has no contraindications. Rectal tubes used as indwelling urethral catheters, or mushroom catheters, may be employed indefinitely in conjunction with tidal drainage in either male or female urethras without producing cystitis or urethritis. They must be removed, cleaned and replaced once a week, and care must be taken to avoid the use of those that are too large.

The incidence of decubitus ulcerations is greatly reduced, and the problem of nursing a patient with an injury to the spinal cord is greatly simplified if the patient is kept dry by the proper use of tidal drainage. The incidence of all types of sepsis of the urinary tract in cases of injury of the spinal cord has been reduced from 73 per cent in 33 cases to 15 per cent in 26 cases through the prompt, intelligent and routine use of tidal drainage in the care of the bladder.

Conditions of the Neck of the Bladder.—MacKenzie and Beck,[67] from a comparison of the 30 specimens of the adult female urethra and the neck of the bladder with 17 similar specimens from children 4 years of age and younger, concluded that chronic inflammation of the urethra and the neck of the bladder is present in a higher percentage

66. Munro, Donald: "The Cord Bladder:" Its Definition, Treatment and Prognosis When Associated with Spinal Cord Injuries, J. Urol. **36**:710-729 (Dec.) 1936.

67. MacKenzie, D. W., and Beck, Sidney: A Histopathological Study of the Female Bladder Neck and Urethra, J. Urol. **36**:414-437 (Oct.) 1936.

of adults than has heretofore been imagined. Perimucosal structures about the neck of the bladder and the posterior third of the urethra are acquired. These structures simulate prostatic tissue because they take origin from the same type of embryologic tissue and thus have the same inherent properties. The stimulus required for the acquisition of these structures may be: (1) infection within the genito-urinary tract, (2) structural anomalies within the genito-urinary tract and (3) trauma at childbirth. These buds and nests, known as von Brunn's cell nests or buds, so far as they are a proliferation of the mucosal epithelium derive their lumens from the intra-epithelial glands, as seen in the mucosal epithelium in children. Those structures about the neck of the bladder and the posterior third of the urethra, referred to by previous workers as prostatic structures, are considered by MacKenzie and Beck to result from a process similar to cystic disease of the upper part of the genito-urinary tract, better known as pyelitis cystica, ureteritis cystica and cystitis cystica, according to location. They propose to call it cystitis cystica when it occurs about the neck of the bladder and urethritis cystica when it occurs in the urethra.

Pilcher [68] reported the case of a woman aged 49 who had a malignant lesion in the bladder situated close to the neck. Complete surgical removal of this lesion necessitated resection of most of the trigon of the bladder and division of the urethra about 1.5 cm. distal to the internal sphincter. Resection of the urethra involved the region that is normally occupied by the external sphincter in the male. The distal end of the urethra was then sutured to the remaining portion of the trigon and wall of the bladder, and the neck of the bladder was reconstructed around a catheter. Convalescence was uneventful. After removal of the suprapubic tube, the suprapubic sinus healed promptly. The patient voided satisfactorily and was not incontinent. Urination was comfortable and under perfect control. A surgical procedure of this type at once raised the question of whether or not incontinence would result. Cabot, in discussing Pilcher's report, stated that there is considerable confusion regarding the external urethral sphincter of the female. Some authors describe the external sphincter as the more powerful of the two and as a thoroughly well defined structure. Other authors doubt the existence of such a structure. Recent microscopic studies of longitudinal sections of the urethra made by Shoemaker failed to reveal definitely placed circular fibers such as are regularly to be found in the position of the external sphincter in the male. The fact that incontinence did not result in this case suggests that the control of the urine after complete removal of the internal sphincter may depend on the

68. Pilcher, Frederick, Jr.: Complete Resection of the Vesical Neck in the Female, Proc. Staff Meet., Mayo Clin. **11**:577-579 (Sept. 9) 1936.

widely scattered circular muscle fibers rather than any well defined muscle group properly described as an external sphincter.

Heitz-Boyer [69] applied the name "inflammatory new growths of the neck of the bladder" to a combination of pathologic conditions at that point which he has been clearly recognizing for the last fifteen years and which appear almost exclusively in the female, corresponding to lesions, often minimal in size, of the urethrocervical region. These new growths, which appear as small eminences of various degrees, not only may lead to intractable cystitis but may result in grave disturbances of the general health of the patient. Of an inflammatory nature and occurring after prolonged infection of, or toxic effect on, the cervico-urethral mucosa, they may be of enterorenal, staphylococcic or venereal origin. They can be diagnosed only endoscopically and can be recognized as representing any one of five different varieties, namely, polypous, cystic edematous or angiomatous or of the nature of an abscess.

Treatment must be surgical and consists of the application of the high frequency current in the form of etincelage, with the author's forked electrode; this is not a cutting current, nor yet an electrocoagulation, both of which are too drastic. Destruction of each eminence may be supplemented at will by electric curettage of the entire neck of the bladder, if there is pathologic change between the individual outgrowths; but this must be done with the greatest care, with control rigorously maintained at low heat. The results are beyond all expectation; in nearly all cases the patients are entirely cured after two or three months of application. When failure results, it is because the new growths were not the primary cause of the trouble but were the result of a neuropathic diathesis.

Rupture.—Dixon and Strohl [70] reported a case of rupture of the urinary bladder. This case serves to emphasize the importance of surgical intervention in acute abdominal disorders when certain signs, such as acute pain and generalized rigidity, are present. The character of the fluid in the abdominal cavity, although it is no different in appearance than that frequently found in cases in which ascites occurs as a result of a variety of causes, suggested the possibility of urine from a ruptured bladder.

The cause of rupture of the bladder in this case is not known. The patient said that he had voided 3 or 4 ounces (90 to 120 cc.) of urine soon after the onset of the acute pain in the upper part of the abdomen and that he had voided before retiring, eight or nine hours previously.

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69. Heitz-Boyer, M.: La maladie néoformante du col de la vessie chez la femme, J. d'urol. **42**:216-251 (Sept.) 1936.

70. Dixon, C. F., and Strohl, E. L.: Spontaneous Rupture of Urinary Bladder, Am. J. Surg. **33**:110-113 (July) 1936.

The urine obtained by passage of a catheter three or four hours before operation evidently came from the abdominal cavity. The edges of the opening in the bladder were ragged and appeared necrotic. They were trimmed until healthy-appearing tissue was reached. Unfortunately, the excised portion of the wall of the bladder was not preserved for microscopic study. Syphilitic ulcerations do have a tendency to occur in the midline; for instance, ulcerations in the midline of the anterior thoracic wall and sternum are seen occasionally. In such instances syphilis has always to be ruled out as a possible etiologic factor. In this case the rupture was in the midline, and obstruction of the neck of the bladder was not a factor, as it previously has been reported to be in some of the cases.

Incontinence.—Lowsley [71] stated that it is possible to cause rupture of the bladder in animals if the urethra is tied tightly with ribbon gut. Ribbon gut tied around the urethra with moderate tightness will cause stricture and accompanying distention of the bladder and thinning of the wall. If the ribbon gut is applied more loosely, the bladder will succeed in emptying itself against pressure, resulting in marked hypertrophy of the musculature and contraction of the bladder. No hydroureter or hydronephrosis resulted from these experiments. The animals were killed or died two months or less after the operation.

In the human being, various muscle transplantations are replaced by the formation of an efficient sphincter by means of ribbon gut, used as an encircling band, a plication suture over the top of the relaxed urethra in the female or as a plication of the membranous urethra in the male. In cases of partial incontinence a cure is effected by encircling the urethra with ribbon gut and tying it snugly. Fibrous tissue replaces the ribbon gut, as was demonstrated by the experiments on animals. The newer plastic operations, made possible by the use of ribbon gut, are more desirable than the older procedures because they make counter-drainage unnecessary, thereby decreasing the period of hospitalization.

Fistulas.—Higgins [72] reported from a review of the literature that vesico-intestinal fistulas are caused more frequently by an inflammatory process than by carcinoma or trauma. Diverticulitis of the bowel is the most frequent etiologic factor. A preliminary colostomy is advisable in cases in which the causative factor of the formation of fistula is diverticulitis of the colon. The most common sites of the fistulas were between the rectum and the bladder and between the sigmoid and the

71. Lowsley, O. S.: New Operations for the Relief of Incontinence in Both Male and Female, J. Urol. **36**:400-413 (Oct.) 1936.

72. Higgins, C. C.: Vesico-Intestinal Fistula, J. Urol. **36**:694-706 (Dec.) 1936.

bladder. A diagnosis may be established by cystoscopic and proctoscopic examination and the employment of cystograms and enemas of barium sulfate. Radical operation is essential in dealing with a fistula associated with a malignant growth. Prognosis depends on the etiologic factors associated with the formation of the fistula. Treatment is essentially surgical.

Drainage.—Boyd [73] stated that suprapubic cystotomy can be performed with the patient under local and field block anesthesia, which is so much safer for the patient who is a poor risk than any type of general or spinal anesthesia. Suprapubic cystotomy insures a dry wound in practically every case, and if there is any leakage, it is slight and can be controlled readily. It nearly always prevents the development of any except mild infections of the wound. It permits decompression of the bladder and opening the bladder when necessary without distention by air or fluid. It prevents postoperative changes in the symphysis pubis and, as far as can be done, the later separation of the muscles with the formation of hernia. It does not require long experience in operations of the bladder.

The essentials in technic are as follows: A midline incision is made. The fat and fascia from the upper, anterior part of the bladder over an area from 4 to 6 cm. in diameter are freed. The incision in the bladder about the tube is closed with interrupted plain catgut sutures. The bladder is infolded for from 2 to 2.5 cm. with a second layer of sutures. The tube then lies in the middle of the closed incision, and the bladder is not sutured tightly about the tube. The bladder is anchored to the abdominal wall if the capacity of the bladder is large. One large silver wire stay suture is used to approximate the rectus muscles. A small rubber tissue drain passing all the way through the abdominal wall should be left in the upper end of the wound. Closure of the lower 2 to 3 cm. of the wound is not done, and a small piece of fenestrated Dakin tube should be left in that part for drainage.

The postoperative care consists of daily dressings wet with acriflavine and continuous or decompression drainage. The upper and lower ends of the wound are gently opened daily with a hemostat for as many days as necessary to insure adequate drainage.

There were no fatalities in a series of 60 cases, even though some of the patients were very ill, and only 1 had an infected wound. A few superficial, unimportant infections developed about the drains. Thrombosis of the iliac vein occurred in 2 very feeble old men. There have been no hernias or other complications.

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73. Boyd, M. L.: Suprapubic Cystotomy for Drainage, J. Urol. **36**:740-755 (Dec.) 1936.

PENIS

Tuberculosis.—Lazarus and Rosenthal [74] reported a case of primary tuberculosis of the penis occurring in a young adult after sexual exposure. Radical amputation of the penis was necessary. This condition is a rare clinical lesion, particularly in adults. Only 25 cases have been reported in the literature to date. The diagnosis is often confused with chancroid, chancre or granuloma inguinale and therefore is made late in the course of the disease. It can be confirmed only by histologic study, preferably by inoculation of an animal. The disease is characterized by a slowly spreading, painful ulcer with an indurated border which has a marked tendency to become undermined and by a central ulceration covered with a yellowish, odorless slough. In the later stages areas of necrosis may be seen near the indurated margin and nodules in the region of the base of the ulcer. The lesion shows a tendency to scar formation, which at times breaks down to form new ulcers and is resistant to all types of treatment. Inguinal adenopathy is generally present but is never an outstanding feature of the disease. Urinary symptoms occur only when the urethra is involved.

In several cases excision or curettage of the lesion associated with the usual hygienic regimen for generalized tuberculosis produced good results. Radical amputation is done in cases in which the glans penis and urethra are extensively involved. The prognosis is favorable in primary tuberculosis of the penis in adults. When it occurs in children after circumcision, the prognosis is unsatisfactory.

URETHRA

Hypospadias.—Walters [75] stated that the most successful operations for hypospadias have been those in which flaps of skin taken from the penis or scrotum have been used to form a skin-lined canal to the end of the penis from the abnormal opening of the urethra. Operations intended to overcome the penile curvature deformity of hypospadias should be undertaken at a very early age, preferably between 1 and 2 years. Ordinarily this correction can be satisfactorily obtained by means of transverse incisions through the fibrous cord occupying the position of the absent penile urethra, one transverse incision being made immediately in front of the abnormally placed meatus and one relatively far forward close to the glans penis, if a second one is required.

There are three types or degrees of hypospadias: (1) perineal, when the abnormal opening is in the perineum; (2) penoscrotal, when it is

74. Lazarus, J. A., and Rosenthal, A. A.: Primary Tuberculosis of the Penis, J. Urol. **35**:361-377 (March) 1936.

75. Walters, Waltman: Successful Operations for Hypospadias, Ann. Surg. **103**:949-958 (June) 1936.

at the root or base of the penis, and (3) penile, when it is in the shaft of the penis. The method of Ombrédanne is applicable to all three types of hypospadias and has the advantage that the penile portion of the flap which is used to form the urethra is free from hair. The principles of treatment of hypospadias, as outlined by Ombrédanne, consist in converting a perineal or penoscrotal opening to a penile opening by elevating a longitudinal flap of skin from the scrotum distal to the urethral opening and reflecting it upward, covering it with lateral flaps taken from the adjacent areas of the scrotum.

In the Bucknall operation a delayed flap of skin is raised from the scrotum, forming the anterior portion of the skin-lined canal, which extends from the penoscrotal or penile hypospadiac opening to the end of the penis. Its greatest value is in cases in which other methods have failed, and this is most likely to be in those in which the patients are adults. Healing takes place without the development of a fistula because of the wide attachment of flaps adjacent to the skin-lined canal and the absence of tension on the anastomosis from erections during convalescence, due to the elasticity of the scrotum.

The Thiersch operation in which parallel flaps are taken from the penis gives excellent restoration of the canal unless a fistula develops. It employs tissue free from hair and of fine texture, which is consequently particularly well suited to its changed environment. Unfortunately, it has been characteristic of this type of operation that the formation of a fistula was a relatively common complication, requiring further operations for its repair, oftentimes with unsuccessful results.

Various stages of the Ombrédanne operation have been used, a total of 88 procedures for 32 patients. It was necessary, therefore, in order to obtain a satisfactory end-result to use an average of three stages. The cases were divided about equally into those of perineal, penoscrotal and penile hypospadias. The results in 28 of the 32 cases were excellent. The Bucknall type of operation has been used in 16 cases, and here likewise the operation has of necessity been divided into two stages, to which has been added narrowing of the urethral orifice by the method of Ombrédanne. The results of operation in these cases were excellent. The Thiersch method and its modifications have been used in 13 cases, 46 different procedures being employed in these cases to complete the operation.

Urethral Glands.—Cabot [76] stressed the conflicting opinions that have existed for a number of years regarding the possibility of lesions of the urethra of the female acting as a focus of infection similar to

76. Cabot, Hugh: Are Glands in the Posterior Urethra of the Female an Important Focus of Infection? Proc. Staff Meet., Mayo Clin. **11**:589-591 (Sept. 9) 1936.

certain lesions of the prostate and cervix. The evidence in regard to the existence of important glandular structures in the proximal two thirds of the female urethra has been inconclusive.

The conclusion from the recent studies of MacKenzie and Beck [77] and of Cabot and Shoemaker [78] on more than 100 specimens removed at postmortem examination was that there are no glandular structures in the proximal two thirds of the female urethra. One of the striking observations in Cabot and Shoemaker's study was the number of very deep crypts in the mucosa, which when seen in cross-section might be mistaken for glandular structures if care were not exercised in studying the arrangement of the cells; these were in fact only simple invaginations of the urethral mucosa.

In the specimens studied a large number of cysts containing albuminous material were found lying beneath the mucosa. According to Cabot, these are the areas which have been referred to by Renner and by Folson as showing what they regarded as corpora amylacea. The cysts were lined with squamous epithelium and showed no evidence of glandlike structures. They appeared to be entirely similar to the structures seen in the well known conditions of pyelitis, ureteritis and cystitis cystica. In other words, they demonstrated that cystic disease, well recognized in other parts of the urinary tract, is very common in the urethra. Papillary outgrowths in the posterior portion of the urethra were frequently noted. That there are many symptom-producing lesions of the female urethra is an undoubted fact, but the evidence does not warrant assuming that such lesions originate from glands or that they can be made the basis for relapsing infection of the urinary tract in the female. The author expressed the belief that the hypothesis advanced by Renner and by Folsom of a major focus of infection in the posterior part of the urethra of the female comparable with lesions of the prostate of the male has no satisfactory basis in anatomic fact.

Urethral Lymphatics.—Parker [79] made a study of the lymph vessels from the posterior part of the urethra and stated that the distribution of the lymphatics from this portion and their regional lymph nodes varied for the most part according to the variations in the pelvic arterial branchings.

In 30 stillborn male infants the lymph channels coursed backward along the main pelvic arteries most frequently to nodes situated along

77. MacKenzie, David, and Beck, Sidney: A Histopathologic Study of the Female Urethra, to be published.

78. Cabot and Shoemaker: Unpublished data.

79. Parker, Alice E.: The Lymph Vessels from the Posterior Urethra, Their Regional Lymph Nodes and Relationships to the Main Posterior Abdominal Lymph Channels, J. Urol. **36**:538-557 (Nov.) 1936.

the pubic branches of the obturator arteries, to nodes of the internal, middle and external chains of the external iliac groups and to hypogastric nodes, and, occasionally, to lateral sacral nodes, to ischiatic nodes of the gluteal region and to superior hemorrhoidal nodes.

The lymph vessels and nodes draining the postpubic portion of the urethra in the female differed somewhat in distribution from those found in the male. The lymph vessels coursed backward along the umbilical arteries, followed branches and trunks of the hypogastric arteries and traversed the pelvic fascia along the lateral borders of the bladder. The regional nodes for the efferent lymph vessels following those courses were nodes of the internal and middle chains of the external iliac groups, hypogastric nodes, lateral sacral nodes and ischiatic nodes of the gluteal regions.

Indirect and direct connections between lymphatics of the posterior part of the urethra and of the wall of the bladder are described. The courses of extension of injected material from the regional nodes through the posterior abdominal lymph channels to the thoracic duct are illustrated. Some of the lymph nodes, found to be regional or intercalated nodes of the efferent lymph vessels of the posterior part of the urethra, are apparently identical with lymph nodes described in the literature as regional or intercalated nodes for other pelvic organs and regions but were never previously connected with this portion of the urinary tract. Most of the regional nodes for the posterior part of the urethra belong to the principal groups of nodes of the pelvis.

Urethral Tumors.—Campbell and Fein [80] reported a case of malignant melanoma of the penile urethra which is a clinical novelty and of special pathologic interest. Sarcoma of the urethra most commonly manifests itself by the appearance of a localized neoplasm at some point along the canal. As the growth enlarges, symptoms of obstruction of the lower part of the urinary tract appear. In 4 of the cases reported in the literature a gonorrheal stricture was erroneously believed to be present. With secondary infection of the tumor, the symptoms were suggestive of periurethral abscess, as they were in the case cited by Campbell and Fein. Inguinal adenitis is attributable to metastasis and to lymphatic absorption from the region of the tumor. As the disease progresses, metastasis elsewhere is likely to be noted, even in the cervical region. Ultimately these patients died of neoplastic toxemia or of renal failure.

The diagnosis of tumor of the urethra is suggested by the history of a periurethral swelling in the absence of local infection. The growth

80. Campbell, M. F., and Fein, M. J.: Malignant Melanoma of the Penile Urethra, with a Brief Review of Urethral Sarcoma in the Male, J. Urol. **35:** 573-582 (May) 1936.

is usually firm. As in this case, regional metastasis may offer a diagnostic clue. Diagnosis may be confirmed by the histologic examination of a small piece of the tumor removed with a biopsy rongeur introduced through a tubular endoscope. This may be accomplished readily without risk or marked discomfort to the patient. Prognosis is almost uniformly hopeless. Wide excision of the growth offers the only posssibility of cure, but because of the high degree of malignancy of these tumors of the urethra and their tendency to metastasize, surgical intervention almost always proves futile. Intensive radiation therapy, either by interstitial implantation or with the roentgen rays, offers the only aid to surgical treatment, but for similar reasons will also fail.

Urethritis.—Gurnee [81] stated that the principles which govern the treatment of gonorrhea in the male should be just as forceful in the female, but because of the absence of pain the tissues are subjected to strong caustics or electric cautery instead of gentle daily manipulation.

Complete shutting off of gonococci results in their death. Curtis has proved this phenomena in tubo-ovarian abscess, and it has been observed to hold true in bartholinitis; the organism dies in about three weeks if there is no exit for the pus. Incomplete drainage of gonococcic pus results in retarded cures.

By means of the Elliott apparatus a consistently uniform temperature of 128 F. can be maintained for any length of time against a large portion of distended vagina, cervix, adjacent parametrium and pelvic organs, thereby clearing up the latent foci of infection which heretofore were so difficult to reach. Fever therapy with the hot cabinet alone gives only a 55 per cent chance of cure of gonorrhea and is a very drastic treatment. Short wave diathermy, while it gives sufficient heat, is extremely dangerous when used in combination with the hot cabinet for fever therapy. Fever therapy can best be given without any serious complications by combining the hot cabinet and the Elliott treatment.

Owens [82] considered that by treatment with artificial fever, prompt and dramatic relief of gonococcic arthritis and acute epididymitis can be promised in every instance. Owens stated that this progress in therapy is most appreciated as it applies to arthritis, which was formerly so painful, time consuming and often permanently disabling.

Acute urethritis of less than two weeks' duration has not responded to fever treatment as well as have the chronic infections with prostatic involvement. This experience suggests the possibility that fever therapy

81. Gurnee, W. S.: Gonorrhea in the Adult: Diagnosis; Elliott Treatment and Hyperpyrexia, Am. J. Surg. **33**:500-508 (Sept.) 1936.

82. Owens, C. A.: The Value of Fever Therapy for Gonorrhea, J. A. M. A. **107**:1942-1945 (Dec. 12) 1936.

alone should not receive all the credit for the apparent cures and that natural resistance in the cases of acute infection has not yet developed the antigenic factors that are probably more active in the cases of chronic infection.

Clinical experience is accumulating to support the laboratory conclusions that certain strains of gonococci may be utterly destroyed by temperature of a degree and duration tolerable to the patient, while other strains are resistant to such temperatures. An increasing number of patients have achieved apparent cure after a single session of six hours at a temperature of 106.5 F., while others receive no appreciable benefit after four sessions.

Given patients who can and will take the treatment, more than 80 per cent of gonococcic infections regardless of complications may be absolutely cured in two weeks. Ability of the patient to take the treatment depends on the condition of the heart, the resistance of the skin to heating and the patient's temperament. Those who are unsuitable for one reason or another constitute 12 per cent in Owens' series.

Urethral Injury.—O'Conor [83] stated that in a period of thirteen years he treated 31 men suffering from traumatic rupture of the urethra. Eight incurred this injury from falling astride a loose manhole cover. He stated that although no mention of injury from this source is to be found in the textbooks, personal inquiry has disclosed that in the larger metropolitan centers it occurs sufficiently often to deserve comment. The blow received by the perineum is especially severe, because the metal cover is swung violently upward and strikes as the body is lurching downward and forward. In the 8 patients so injured, the posterior bulbous urethra, close to the triangular ligament, received the impact. In none was the pelvis or other bones fractured. When the urethral floor is so severely traumatized that continuity is destroyed, the proximal (vesical) portion is retracted and elevated by the pull of the strong fascial attachments to the urogenital diaphragm. The extent of the separation of the torn urethral edges depends largely on whether the floor of the urethra is severed or whether the roof alone is torn across. If the floor alone is injured and the roof of the urethra is intact, one may be fortunate enough to guide a small, soft rubber catheter (Wishard), passed over a fairly rigid stylet, by careful and close adherence to the roof of the urethra during the insertion. When this procedure is successful, drainage of the bladder is supplied by the indwelling catheter, and unless there has been perineal extravasa-

83. O'Conor, V. J.: Repair of Rupture of the Male Urethra, with Report of Eight Injuries from Falling Astride a Manhole Cover, Surg., Gynec. & Obst. **63**:198-200 (Aug.) 1936.

tion or marked hemorrhage, no incision is necessary. If perineal extravasation or hemorrhage has occurred, single or multiple incisions in the perineum with adequate provision for drainage will suffice, and the urethral lumen will restore itself along the indwelling catheter.

Except in instances of crushing injury of the floor of the urethra without separation of the urethra at the point of injury, catheterization, even carefully and expertly done, is rarely possible. It should be emphasized that repeated unsuccessful attempts at catheterization only increase the local injury and add to the dangers of increased hemorrhage and deep-seated infection.

In all cases of rupture of the urethra from external violence, the ease of repair and the rapidity of recovery depend largely on the avoidance of unsuccessful catheterization and the recognition of the necessity for immediate surgical intervention.

Until recently O'Conor favored the perineal approach in draining the bladder and in attempting properly to restore the urethral lumen. Although patients so treated did well and usually enjoyed a somewhat shorter period of hospitalization than those treated suprapubically, the resultant perineal and urethral scarring was always considerable and necessitated frequent and repeated urethral dilation for a prolonged period. The method now preferred is extraperitoneal cystotomy, with retrograde splinting of the urethra by an indwelling catheter and perineal incision only when necessary to drain extravasated blood and urine. This splinting is accomplished by the use of interlocking sounds which are passed simultaneously through the posterior and the anterior part of the urethra and joined in such a way that the urethral sound may be guided safely into the bladder. A no. 22 French soft rubber catheter is then stitched securely over the end of the urethral sound and withdrawn through the urethra. The catheter is properly fixed in the urethra, and the bladder is closed in the usual manner with a small mushroom catheter in the dome for immediate drainage. The urethral catheter is closed for a period of from five to seven days, suprapubic drainage being allowed during this time. The urethral catheter is then opened, the bladder is irrigated and the suprapubic tube is removed. There is rarely any suprapubic leakage of urine after this time, as drainage is adequately supplied through the urethral catheter. This is removed when the suprapubic wound seems firmly healed, usually on the twelfth to the sixteenth day after operation. The complete restoration of normal urinary function and the subsequent lack of urethral stricture are the obvious advantages of this method. These patients require occasional urethral dilation, to be sure, but they do not present the serious problem of potential stricture that is almost invariably present after perineal urethrotomy.

TESTIS

Ectopia.—Deming,[84] after a series of experiments with monkeys, stated that the gonadotropic factor is a definite aid preceding and following surgical treatment of the undescended testis. It enlarges the inguinal canal and the cord and renders the testis more movable in the monkey. Treatment may be instituted in the human being as early as 2 years of age. The earlier the treatment the better are the chances for a normally functioning testis. The histologic picture in the monkey six weeks after the cessation of the administration of the gonadotropic factor persists with negligible change.

Woodruff and Milbert[85] reported a case of strangulation of an undescended testis by a loop of omentum. It represents a rare and previously unrecorded complication threatening the safety of the maldescended organ. Etiology, pathology, symptomatology, diagnosis and treatment are discussed as they pertain to the condition in question. In this instance it is rather ironical that the omentum, so frequently referred to as the "policeman of the peritoneal cavity," should have wandered astray to become the "hangman" of the testis.

Cysts.—Abell[86] reviewed cysts of the testis, excluding hydroceles of the tunica vaginalis, encysted hydroceles of the cord and those occasionally noted in the body of the testis proper; they arise within epididymal structures or vestigial remnants connected with them. Abell observed 32 instances of cysts conforming to this in origin and site.

Four patients gave a history of trauma with the appearance of the tumor immediately thereafter. One other stated that the tumor appeared after the wearing of a truss and still another that it developed after an operation for hernia.

The size was noted in 26 cases; the smallest tumor was 1 inch (2.5 cm.) in diameter, and the largest measured 8 by 4 by 4 inches (20 by 10 by 10 cm.); the size of the remainder varied between these limits. Twenty-five of the 32 patients came to operation, the character of the growth being unilocular in 12 cases, multilocular in 9 and polycystic in 4; 21 were unilateral and 4 were bilateral; 3 were enclosed within the tunica vaginalis or were intravaginal, and 22 were extravaginal. Twenty-six operations were done on 25 patients, 1 patient returning after fourteen years with recurrence of the cyst in the site of the former operation.

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84. Deming, C. L.: The Gonadotropic Factor as an Aid to Surgery in the Treatment of the Undescended Testicle, J. Urol. **36**:274-288 (Sept.) 1936.

85. Woodruff, S. R., and Milbert, A. H.: Strangulation of the Undescended Testicle by a Loop of Omentum, J. Urol. **36**:558-563 (Nov.) 1936.

86. Abell, Irvin: Cysts of the Testicle, Ann. Surg. **103**:941-948 (June) 1936.

The pathologic report revealed polycystic disease in 4 cases, which was bilateral in 2 and unilateral in 2. Specimens from 1 case of bilateral polycystic disease were unusually large, measuring 170 by 60 by 40 mm. and 150 by 50 by 30 mm., respectively. Of the specimens from the cases of bilateral involvement, only 1 showed recognizable epididymal tubules, being composed of pale pinkish gray fibrous and serous tissue containing many simple thin-walled cysts clumped together in masses. The cysts varied in size, measuring from 2 to 40 mm. in diameter, and contained clear, colorless fluid. The unilateral specimens were similar in character. In some of the cysts the walls were hyalinized and vascularized and revealed lymphocytic infiltration.

These cysts may be considered as falling in three groups: (1) cysts having their origin in vestigial remnants, (2) retention cysts and (3) polycystic growths or cystic embryomas.

URINARY CALCULI

Gray [87] reported a series of clinical cases of stone in the urinary tract from the Lester Chinese Hospital in Shanghai. He stated that infection played little part in the etiology and that it certainly is not an essential feature. The reaction of the urine has also not been of great significance. In the experimental cases, although the tendency has been for the urine to become alkaline, stone may form before this happens.

The two positive findings which have been observed throughout the study have been: (1) some alteration in the metabolism, so that the urine may be considered to be supersaturated with stone-forming substances and the formation of sediment would therfore be likely, and (2) a local factor in the urinary tract. It is felt that the latter probably acts by altering in some way the colloid conditions, so that the sediment becomes a concrement. It is suggested that in most cases this factor has been some alteration in the integrity of the epithelial lining of the tract. Such a change may easily be produced experimentally by trauma, obstruction, perhaps infection, devitalization by means of injury to the vascular supply, chemical irritation and a diet deficient in vitamin A. The last-named factor needs to be of a severe grade, but if it is it will produce a series of changes of which the last stage is keratinization. Formation of stone may occur in the presence of either of these factors singly, but much more readily in the case of the second. In the clinical cases it is felt that such alterations in the epithelium might well occur, and a number of biopsies of the mucosa of the bladder have been made. With the exception of 2 cases, however, although changes have been noted, they have not approached the

87. Gray, J.: Urinary Stone Formation, Clinical and Experimental, Chinese M. J. **50**:761-786 (June) 1936.

severity of those obtained by experimental means, especially by the diet deficient in vitamin A. Neither has there been any other evidence in a survey of the diet or in the clinical condition of the patients to suggest more than at most a slight deficiency in vitamin A. However, it was shown experimentally that with the diet stone may form before the epithelial change has progressed as far as as keratinization. This was particularly true if an excessive quantity of vitamin D had been added to the diet.

As a large number of the patients have been children or members of the laboring class who work in the open without many clothes, it was felt that the possibility of a moderate excess of absorption of vitamin D must be considered, or perhaps a combined deficiency of vitamin A with an excess of vitamin D. Apart from this, although the number of clinical cases investigated is not yet large enough, the evidence does not point strongly to a deficiency of vitamin A of any severe grade.

The effect of polishing rice, particularly in regard to the possibility of calcium dust being mixed with the food, is felt to be of importance in Eastern countries.

Hou,[88] in his experiments on albino rats, showed that the addition of vitamin D to a diet which was deficient in vitamin A and in fat increased the incidence of urinary calculi and the removal of vitamin D decreased it. Alteration of the protein content of the diet also affected the frequency of formation of urinary calculi. Both a high and a low casein content resulted in an increase in the number of cases of calculi up to 100 per cent. Chemical analysis of the proteins for calcium and phosphorus indicated that the result was not due to an unbalanced calcium and phosphorus ratio. A lowering of the inorganic calcium and phosphorus in the diet caused an increase of the incidence of urinary calculi. The addition of heated lard caused a decrease in the frequency of calculi. Rats on the diet low in calcium and phosphorus, however, showed an increase.

In general, among the different groups studied the occurrence of calculi appears to run parallel to the presence of infection or of severe changes in the epithelium of the kidney and the urinary bladder. The presence of calculi in the kidney or in the bladder bears some definite relation to the type of diet used.

The calculi found in the various groups studied consisted mainly of triple phosphates.

Snapper, Bendien and Polak[89] stated that urine contains many salts and compounds in solution, some of which are hardly water

88. Hou, H. C.: The Influence of Diet on the Formation of Urinary Calculi, Chinese M. J. **50**:787-796 (June) 1936.

89. Snapper, I.; Bendien, W. M., and Polak, A.: Observations on the Formation and the Prevention of Calculi, Brit. J. Urol. **8**:337-345 (Dec.) 1936.

soluble, such as uric acid and calcium oxalate. This condition is brought about by two factors: (1) the hydrotrophic action of certain substances, such as urea and hippuric, salicylic and mandelic acids, which further the solubility of insoluble salts, and (2) the presence of colloids. For example, 100 cc. of water will dissolve 0.63 mg. of calcium oxalate, while 100 cc. of a 3 per cent solution of urea will dissolve 1.28 mg. Likewise 100 cc. of water will dissolve 0.8 mg. of calcium carbonate, while a like amount of 15 per cent sodium salicylate will dissolve 5 mg. The benzoates, hippurates and mandelates have the same property.

In the development and growth of renal stones, precipitation of flocculation of the colloids which form the nucleus and frame of the stone is more important than the precipitation of salts, which is secondary. Therefore, calculogenesis and growth may be inhibited by stabilizing the urinary colloids; without precipitation of the colloids no renal stone can develop or increase in size. The authors have shown that in vitro the salicylates will prevent precipitation of different colloids by aluminum sulfate, and that other salts, such as the hippurates, the benzoates and the mandelates, are less effective in this respect. Because hippuric acid has the property of hydrotrophy and also inhibits flocculation of colloids, the authors considered that its presence in the urine assumes new importance.

In experimental calculosis brought about by the use of a standard diet with vitamin A but with large amounts of calcium carbonates (3 per cent) they prevented the formation of stones by the use of large amounts of sodium benzoate, which is excreted in the urine linked with amino-acetic acid as hippuric acid. They also cleared up clinical phosphaturia without changing the reaction of the urine by giving 6 Gm. of sodium benzoate daily. They attributed this to the hydrotropic property of hippuric acid and concluded that the use of this substance is a rational measure in preventing recurrent calculi. Hippuric acid was used because it is a physiologic constituent of the urine. Other stabilizing and hydrotropic substances, such as the salicylates and mandelates, may give even better results.

Kretschmer [90] reported that of 21 children with stone in the urinary tract, 4 did not undergo treatment. Three of these passed stones spontaneously. The fourth was a girl with a large stone in the kidney, for which surgical intervention was advised but was refused.

In 5 cases stone was removed from the kidney by pyelolithotomy and in 1 by nephrolithotomy; in 2 cases resection of the kidney was also carried out. The patients with stone in the ureter were treated by

90. Kretschmer, H. L.: Stone in the Urinary Tract in Children: A Critical Study of Twenty-One Cases, Am. J. Dis. Child. **52**:513-527 (Sept.) 1936.

ureterotomy. Five of the patients with stone in the bladder were treated by suprapubic lithotomy, and 5, by litholapaxy. There were no deaths and no postoperative complications.

The indications for the treatment are the same in the child as in the adult. If the stones are small enough to pass, if they produce only slight evidence of obstruction or none at all and if infection is mild or absent, medicinal management is justifiable, that is, the administration alternately of urinary antiseptics and alkaline diuretics. The child should be encouraged to drink large quantities of water, milk, lemonade and other liquids. When the stone in the kidney or the ureter is large, so that it produces definite obstruction, or when there is profuse blood, infection or repeated attacks of renal colic, the patient should be operated on.

SURGICAL TREATMENT FOR UROLOGIC CONDITIONS

Priestley and Counseller [91] stated that during 1935 there were 764 patients with urologic conditions on whom 917 operations were performed. These 917 operations included 1,555 surgical procedures. There were 14 deaths in the entire group, or a mortality of 1.8 per cent of the total patients operated on. Hydronephrosis, nephrolithiasis and tumors constituted most of the conditions for which operation was performed. Included in this group were certain patients with far advanced disease. Conservative surgical procedures in selected cases of hydronephrosis are now fairly well standardized and yield satisfactory results in the majority of cases. Nephrolithiasis is a condition which still presents many problems, especially regarding etiology and the prevention of recurrence. In this series 32 renal tumors were removed without a death. Some very large neoplasms were extirpated satisfactorily after preliminary roentgen therapy. Occasionally the anterior approach to the kidney was employed.

Of 57 patients with ureteral lithiasis, transurethral manipulation of the stone or stones was performed on 44 per cent and ureterolithotomy on the remainder. Rather definite indications exist for each procedure, and the best results are obtained by judicious selection of patients for each method. Transplantation of one or both ureters to the sigmoid colon was performed on 13 patients because of various lesions of the bladder, with 2 deaths. Three patients were subjected to transplantation of one or both ureters to the skin with complete recovery.

Forty-two patients underwent suprapubic operations on the bladder, with 2 deaths. Twenty-seven of the 42 patients were suffering from carcinoma of the bladder. It is interesting to note that total cystectomy

91. Priestley, J. T., and Counseller, V. S.: Review of Urologic Surgery for 1935, Proc. Staff Meet., Mayo Clin. **11**:801-804 (Dec. 16) 1936.

for carcinoma was performed on 4 patients without a death. During 1935, 695 patients were subjected to transurethral resection of the prostate gland, whereas prostatectomy was performed on only 2. Cystostomy as a procedure preliminary to transurethral resection was performed on only 3 patients.

A total of 865 surgical procedures were performed on the external genitalia. In many instances multiple surgical procedures were performed on a single patient, especially for certain congenital anomalies which required plastic repair. The surgical treatment of undescended testes gives good results in the majority of cases, whereas experience with the hormonal treatment of this condition has not been so uniformly successful. Determinations of the gonadotropic substance in the urine have been of value in the treatment of patients who have testicular tumors, especially during the postoperative period. The authors trust that the ensuing year will settle some of the existing problems in this field of surgery and open new fields for further advances.

Seventy patients who had carcinoma of the bladder underwent treatment last year. Thirty-three per cent were treated by the suprapubic approach only. In 4 the urine was diverted above the bladder, in 3 by ureterosigmoidal anastomosis and in 1 by bilateral ureterostomy, followed by total cystectomy, without the death of any patient. Cabot has shown previously the simplicity of the technic used in performing bilateral ureterostomy and the low surgical risk. It should be possible, therefore, in treatment of some of the more advanced lesions, to perform bilateral ureterostomy and later total cystectomy and to follow these procedures by radium therapy.

By the methods used today, when preparing a patient for operation on the colon by means of injections of vaccines intraperitoneally, cleansing the bowel and special diets, it is possible in a greater number of cases successfully to transplant the ureters to the sigmoid colon and later to perform the radical operation of removal of the involved bladder.

Whenever a ureter is dilated and the walls are thickened by infection, ureterosigmoidal anastomosis should not be considered. In such cases cutaneous ureterostomy is the operation of choice. One other fact that militates against radical removal of the bladder and diversion of the urinary stream in many cases in which the lesion is of a high grade of malignancy is that metatasis to the regional lymph nodes has been discovered oftener than previously was suspected.

TRANSURETHRAL MANIPULATION

Thompson [92] stated that before the advent of the resectoscope the complete destruction of an epithelioma of the bladder of a diameter much

92. Thompson, G. J.: Transurethral Operations: Changing Conceptions During the Past Five Years, J. A. M. A. **107**:1954-1958 (Dec. 12) 1936.

greater than 1 cm. involved repeated electrocoagulation of the growth at intervals of from a week to a month. The cutting loop of the resectoscope has been found to be a satisfactory instrument for the rapid removal of many tumors of a pedunculate or relatively noninfiltrating type. The bulk of the growth can be rapidly removed with the cutting current, after which the pedicle or base can be thoroughly destroyed by electrocoagulation.

In some cases, particularly in those in which microscopic study reveals a high grade of malignancy, it is well after removal of the tumor to implant radon seeds in the underlying wall of the bladder. In certain cases in which the extent of the lesion or the general condition of the patient has precluded radical surgical removal, this method, combined with subsequent roentgen therapy, has resulted in remarkable palliation, and in some instances it apparently has resulted in a cure.

At the Mayo Clinic during the period from 1932 to 1935 inclusive, tumors have been destroyed in 191 cases by the methods outlined, practically always at one sitting. The results to date from such treatment have been gratifying, on the whole, although sufficient time has not elapsed to warrant final conclusions concerning the efficacy of the method.

Litholapaxy has been advocated for many years for the removal of calculi in the urinary bladder. The presence of a considerably hypertrophied prostate gland was always deemed a contraindication to litholapaxy. Thompson has previously reported a series of cases in which he was able to crush and remove large calculi and, using the same anesthetic, to resect the obstructing portion of the prostate gland. The greatest amount of tissue removed in any case was 47 Gm. It is important that litholapaxy be performed rapidly; hence a lithotrite of the Bigelow type is used by preference. As a general rule it is best to crush the stone prior to prostatic resection, but if the lithotrite cannot be passed easily beyond the prostatic enlargement, it may be necessary to perform prostatic resection first. During the past four years 161 patients with vesical calculi have been treated by conservative transurethral methods at the Mayo Clinic.

Bumpus and Thompson in 1930 reported on a clinical study of 1,001 cases of ureteral calculi; in 60.7 per cent of cases in which a calculus occurred in the lower part of the ureter it was removed by transurethral methods. In most of the cases in that series more than one attempt was made before the stone was obtained, and many times it was not passed until a number of days subsequent to manipulation. During the years 1932 to 1935 inclusive, stones have been removed from the ureter by transurethral methods in 180 cases at the Mayo Clinic; in the large majority of cases the first attempt was successful, the calculus being

removed at the time of the operation, either by engagement with an extractor or by the safer method of enmeshing it with multiple catheters. An attempt to force an extractor into a small ureter may result in perforation and certainly will cause sèvere reaction. One should prefer to insert two or three catheters alongside the stone and leave them in place for from forty-eight to seventy-two hours. Twisting the catheters at that time will often be more profitable than doing so immediately after they are placed.

Prostatic calculi often do not produce symptoms. Hence, Thompson has practically always disregarded their chance finding by routine roentgenographic study. However, when either for local or for focal reasons it is essential to reduce or eliminate the prostatitis which generally is found in association with prostatic calculi, it is not a difficult task to remove the stones by transurethral incision. Thompson prefers to use the Collings knife, for one can gage the depth of the incision, making it no deeper than is actually necessary to expose the nests of stones. Such operations must always be done with thorough recognition of the fact that the procedure is a minor one as far as the patient is concerned but that lack of caution on the part of the surgeon may easily result in a major complication, if not in death. In 8 cases Thompson has incised acute prostatic abscesses with the Collings knife, thus evacuating a large pocket of pus through the urethra.

There has been no mortality from any of the transurethral procedures described, except in the form of cases in which prostatic resection was performed. Of 1,987 patients subjected to transurethral resection for either benign or malignant involvement of the prostate gland during the years 1932 to 1935 inclusive, only 14 died, a mortality of 0.70 per cent.

INFECTION OF THE URINARY TRACT

Frisch [93] reported 47 cases of pyelitis due to colon bacillus in which bacteriophage was employed therapeutically, in all of which the condition had proved resistant to other methods of treatment. The lysin was injected into the renal pelvis, and in 2 children a subcutaneous injection was made also. The method of preparation and administration of the bacteriophage is described.

In 30 of the 47 cases cure was effected, and the urine was sterile after the treatment. In 6, there was improvement. In 6 cases the colon bacillus was resistant to the lysin during the treatment, and in these cases improvement did not occur. Five of the patients discontinued treatment before being cured.

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93. Frisch, Bruno: Ueber das Phänomen der Bakteriophagie in der Urologie, Ztschr. f. urol. Chir. u. Gynäk. **42**:199-205, 1936.

Frisch considered bacteriophage a valuable adjunct to other methods of treatment.

Cook [94] stated that during recent years urologists have realized the value of a most careful bacteriologic investigation of the urine in cases in which infection is suspected. The simple Gram stain of urinary sediment, supplemented by culture of the urine, usually yields information of the greatest value in arriving at the proper diagnosis and is also of value in suggesting the best method of treatment. Repeated examinations are frequently necessary, especially in cases of coccic infection. It is emphasized that one organism may completely check the growth of another, the second organism coming into prominence only after the first has been partially or completely destroyed. The more common infections of the urinary tract, excluding tuberculosis, can be divided into two main groups, namely, those produced by a bacillus and those produced by a coccus. Cook is concerned with a third group of cases, however, in which no organisms can be found even after careful study. He referred to a group of patients who have definite urinary symptoms and who respond to the ordinary methods of treatment of infection in the urinary tract, but positive cultures of the urine are never obtained, although various degrees of pyuria are present. In these cases it is of prime importance to exclude tuberculosis. This is accomplished by the use of cystoscopy, urographic data, repeated examinations for acid-fast bacilli and inoculations of guinea-pigs with urine from the bladder and kidneys. The etiology of this group of cases in which specific organisms cannot be found is obscure. Almost invariably the disease has been present for months or even years, and local symptoms are well marked. Frequent urographic examinations suggest inflammation of long standing. Results of treatment, however, are ordinarily gratifying if renal function remains satisfactory. It may be necessary to continue treatment over a period of from six to eight weeks before improvement is noted. At the beginning treatment consists of lavage of the bladder with potassium permanganate (1:8,000) alternating with a solution of acetic acid (1:3,000) and followed by the instillation of silver iodide. The ketogenic diet is usually employed aided by acidification of the urine by the administration of ammonium nitrate or ammonium chloride in doses of 6 Gm. daily, if necessary, on the third or fourth day of the diet. Intravenous injections of neoarsphenamine are given at intervals of five days until from two to four injections have been administered. Careful search for foci, with eradication of these when present, is perhaps one of the most important factors in treatment. This includes

94. Cook, E. N.: Infections of the Urinary Tract of Obscure Etiology, J. Urol. **36**:460-466 (Oct.) 1936.

investigation of the teeth, tonsils, prostate gland and cervix uteri. The author reported 4 illustrative cases in detail. It is emphasized that no single method of treatment has been uniformly satisfactory and that a combination of all forms of treatment considered has ordinarily yielded the best results. It seems that this group of cases represents a definite clinical entity.

Dillon [95] stated that foci of infection play an important part in the causation of infections of the urinary tract. In vague septic conditions more attention must be paid the urinary tract as a possible site of infection, in spite of negative results of clinical examination of the urine. Dentists should be taught to recognize more of the medical and surgical aspects of an infected alveolar process. Before condemning the patient with symptoms referable to the bladder and "clear urine" as neurotic, larger quantities of urine from the bladder should be sent to the bacteriologist with the request that the examination be made on the concentrated sediment of the entire specimen. Children should be watched more closely during the tooth-cutting age and attention given to dental care and hygiene. Also, during septic reactions the urinary tract should not be forgotten, and more exacting examinations should be made for the presence of bacteria in the clear urine.

URINARY ANTISEPTICS

Cook and Buchtel [96] in the past nine months have given mandelic acid to more than 250 patients. Early results indicated that it was effective in approximately 50 per cent of cases, but more recently, with more careful management, the percentage of good results has been greatly increased. For the most part sodium mandelate in a 10 per cent solution was used. A dose of 1 ounce (30 cc.) before each meal and at bed time was employed, and an acidifying drug, such as ammonium nitrate or ammonium chloride, was usually given. The intake of fluid was reduced to 1,200 cc. daily. In a series of 75 cases in which this drug was employed the urine became sterile in 61 cases, or 81 per cent. In attempting to obtain the desired acidity of the urine without the use of an additional acidifying drug, ammonium mandelate has been satisfactorily employed, following the suggestion of Holling and Platt. Only 1 patient in 15 required a secondary acidifying drug. In order to obtain the best results extreme care and alertness must be used in managing this form of treatment. The urinary p_H must remain below 5.5. Occasionally it will be necessary to employ dietary measures in addition to

95. Dillon, J. R.: Urinary Tract Infection with "Clear Urine," California & West. Med. **45**:489-491 (Dec.) 1936.

96. Cook, E. N., and Buchtel, H. A.: The Use of Mandelic Acid for Infections of the Urinary Tract, Proc. Staff Meet., Mayo Clin. **11**:538-540 (Aug. 19) 1936.

acidifying drugs in order to obtain the desired urinary p_H. In certain cases mandelic acid has been used in conjunction with a ketogenic diet with satisfactory results. To the present time this drug seems to be the most useful in treating bacillary infections and can be used in cases of gout, duodenal ulcer or diabetes mellitus with much less risk than the ketogenic diet. The authors stated that care should be utilized in administering the drug to aged patients or if renal function has been reduced, as it may cause a temporary detrimental effect on renal function. Less than 1 per cent of the patients complained of nausea or vomiting while mandelic acid was being administered. About 10 per cent complained of mild diarrhea, although occasionally the diarrhea was so severe that it was necessary to cease administration of the drug.

Cook,[97] because of certain unpleasant reactions and unsatisfactory results in the treatment of infections in the urinary tract by means of the ketogenic diet, has endeavored to find an adjunct to this method of treatment which will enhance the efficacy and alleviate the distressing complications. Fuller has demonstrated that the product necessary in the urine of patients on a ketogenic diet to render the urine bactericidal is beta-hydroxybutyric acid. Fuller suggested the use of this substance by mouth and recorded a small increase in the beta-hydroxybutyric acid content of the urine after the oral administration of 1 Gm. of this substance three times a day. This suggested the possibility of the oral, intravenous and local use of this substance as an adjunct to ketosis.

The oral administration of synthetic racemic beta-hydroxybutyric acid will definitely increase the urinary excretion of this substance when the patient to whom the drug is given is in a state of sufficient ketosis. There is no effect when the substance is given to a patient who displays little or no ketosis.

The local use of a 2 per cent solution of beta-hydroxybutyric acid buffered to a p_H of from 4.4 to 4.5 has proved beneficial in those cases in which the results with the diet have been unsuccessful or in which the patient has been unable to stand the dietary regimen. Seven of the 10 patients so treated gave negative urinary cultures. In 2 of the remaining 3 patients, symptoms were markedly relieved, while 1 patient obtained no benefit.

The sodium salt of beta-hydroxybutyric acid, when given orally, will produce an increase in urinary excretion of the acid but apparently to a less degree than oral administration of the pure acid.

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97. Cook, E. N.: The Use of Beta-Hydroxybutyric Acid and Certain of Its Salts as an Adjunct in the Treatment of Infections of the Urinary Tract, J. Urol. **36**:289-297 (Sept.) 1936.

The calcium salt of the beta-hydroxybutyric acid was given intravenously in 3 cases. In none of these was an appreciable change noted in the urinary concentration of the acid.

Helmholz and Osterberg [98] recalled that they previously presented data to show that oxybutyric acid appears in the urine as the result of incomplete combustion of fats when only small amounts of carbohydrate are given in the diet. This so-called ketogenic diet is difficult for many patients to take. Recent work, originating with Rosenheim in England, has demonstrated that mandelic acid when taken orally escapes metabolism or conjugation in the animal organism and is excreted in the urine by the kidney in a concentration sufficient for bactericidal action, provided the p_H of the urine is lowered simultaneously. In man, after the oral ingestion of 5 Gm. of sodium mandelate in one dose, 80 per cent of the ingested mandelic acid appears in the urine within twenty-four hours, and the maximal excretion occurs approximately two hours after ingestion. When 3 Gm. of mandelic acid in the form of a 10 per cent solution of sodium salt is given four times during the day, there is a cumulative excretion of the acid as various quantities are ingested, and although diuresis may be produced, the concentration of the acid reaches a value in excess of 1 per cent. By administering ammonium chloride and mandelic acid together, the p_H of the urine can be lowered to approximately 5.0 over a period of many days, while a concentration of 1 per cent mandelic acid is maintained in the urine. These values have been shown to be most effective in sterilizing the urine. If from 0.25 to 1 per cent mandelic acid can be maintained in the urine, the acid will act bactericidally on most organisms at a p_H ranging from 5.0 to 5.7. Certain strains of Aerobacter and Pseudomonas are far more difficult to kill than is Escherichia coli.

Carroll, Lewis and Kappel [99] reported a clinical experience with 50 cases of pyuria in which mandelic acid was administered as suggested by Rosenheim. An analysis of their results shows 37 cases of infection due to the colon bacillus, including acute and chronic pyelitis, pyelonephritis, diverticulum of the bladder, nephroptosis, renal calculi, prostatic hypertrophy with retention and cystitis. In all these, the urine became microscopically clear under the treatment. In 7 cases the urine yielded positive cultures. The average number of days of treatment required to produce sterile urine was seven. Although the condition of 7 patients with coccic infections improved, the urine did not become

98. Helmholz, H. F., and Osterberg, A. E.: Rate of Excretion and Bactericidal Power of Mandelic Acid in the Urine, J. A. M. A. **107**:1794-1796 (Nov. 28) 1936.

99. Carroll, Grayson; Lewis, Bransford, and Kappel, Louis: Mandelic Acid as a Urinary Antiseptic: A Clinical Study, J. A. M. A. **107**:1796-1799 (Nov. 28) 1936.

sterile. In only 1 of 6 cases of infection due to Bacillus proteus was the urine made sterile. The proteus organism is the most resistant to elimination from the urinary tract. In 81 per cent of all cases of colon bacillus infection in which this manner of treatment was employed, the urine was sterile. The authors concluded from this survey that a urinary infection due to the colon bacillus group in which a p_H of 5.5 is maintained may be expected to clear up with the administration of mandelic acid within from four to twelve days. They further emphasized that pyuria is only a symptom and that complete urologic examination should always precede therapy with mandelic acid. The original causative factor in producing the pyuria must be recognized and treated together with the administration of the acid. Caution must be exercised in giving the proper dosage for fear of poisoning. Persons with lowered renal function should not be given mandelic acid.

URINARY EXTRAVASATION

Char, Shih and Yang [100] reported 30 cases of extravasation of urine from the Peiping Union Medical College Hospital. They stated that the most common cause of extravasation of urine is a urethral stricture caused by gonorrheal infection. The urethra proximal to the stricture gradually becomes dilated and weakened because of increased pressure and secondary infection. Rupture eventually occurs with escape of urine into the adjacent tissues. The next cause in order of frequency is trauma to the perineum or a fall astride a hard object. In 3 cases a stone was found in the urethra. The extravasation in these cases apparently was not caused by a stricture but by obstruction attributable to the stone. Occasionally in cases of severe phimosis of long duration, when the preputial opening has been reduced to the size of a pinpoint, extravasation may take place through ulceration of the inner surface of the prepuce. In such cases the urine will extravasate first into the penis and then into the scrotum.

The clinical picture of extravasation of urine is determined principally by the situation of the extravasation, the rapidity with which it occurs and the virulence of the invading organism. If extravasation is rapid, as in the case of a direct injury to the perineum or a fall astride a sharp object resulting in complete division of the urethra, the presenting symptoms will be sharp pain at the site of the injury, bleeding from the urethra, swelling in the perineum and inability to urinate.

Since extravasation is an urgent condition, treatment should be instituted as soon as possible. The treatment should aim to overcome

100. Char, G. Y.; Shih, H. E., and Yang, C. P.: Extravasation of Urine, Chinese M. J. **50**:807-820 (June) 1936.

uremia, to provide adequate drainage and to release the stricture or repair the injury to the urethra.

Seven patients in this series died in the hospital, giving a mortality of 23 per cent. Two patients left the hospital against advice and died shortly afterward. If all the fatal cases were considered together, the mortality would amount to 30 per cent. Eight of the 9 fatal cases were from the group of cases of gonorrheal stricture, and in only 1 of these cases did death follow traumatic injury of the urethra. The deaths were mainly attributable to three factors: 1. The patients came late for treatment when the degree of acidosis and uremia was extreme. 2. The extravasation was extensive and complicated by infection by virulent organisms. 3. The distended urinary bladder was probably emptied too suddenly at the time of operation.

Negley[101] stated that the mortality from urinary extravasation is unbelievably high in persons after the age of 40. The duration of the disease is an important factor in determining the prognosis. The longer extravasation occurs, the more virulent is the infection and the less chance for recovery. Cystotomy, with incision and drainage, seems to be the operation of choice and carries the lowest mortality. Bisection of the scrotum seems in some way to detract from chance of recovery and to add to the mortality unless accompanied by other incisional drainage. The causes of death in order of frequency are septic toxemia, pyelonephritis and cardiac failure, and in most cases degeneration of kidneys, liver and spleen is associated. Periurethral, scrotal, penile, abdominal and phlegmonous processes may occur without urinary extravasation and may be entirely bacterial with exudate.

DIVERSION OF URINARY STREAM

Cabot[102] discussed the three common procedures for diverting the urine above the level of the bladder, namely, nephrostomy or pyelostomy, uretero-enterostomy and cutaneous ureterostomy. The general indications, technic and postoperative care for each procedure are considered.

Nephrostomy seems preferable to pyelostomy, except for temporary drainage, because it is more effective. Drainage is more complete and continuous and there is no leakage. Furthermore, displacement of the tube is more readily avoided, and if necessary nephrostomy may be utilized as a method for permanent drainage. Properly performed nephrostomy does not involve significant injury to the renal parenchyma.

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101. Negley, J. C.: Urinary Extravasation, California & West. Med. **45**:38-41 (July) 1936.

102. Cabot, Hugh: The Methods of Diverting Urine Above the Level of the Bladder, with Particular Reference to Problems of Technic, J. Urol. **35**:596-609 (June) 1936.

A fistula after nephrostomy is practically unknown, whereas it occurs more frequently after prolonged drainage by pyelostomy. The author discussed several different technics for performing nephrostomy and suggested that the method described by Cabot and Holland in 1932 is the most desirable. It is emphasized that in utilizing this procedure it is unnecessary to mobilize the kidney to any great extent except on its posterior surface. This technic involves insertion of an instrument, such as a uterine sound roughly curved in the shape of a U, through the pelvis and lower calix to the desired point on the cortical surface of the kidney. A linen suture is then tied around the bulbous end of the sound, which is pulled back through the pelvis. The suture is removed from the sound and secured on the end of a Malécot catheter, which has been previously cut to a taper; it is then pulled by the linen suture through the pelvis of the kidney and out the lower calix so that the tip of the catheter is accurately placed in the renal pelvis. Nephrostomy performed in this manner involves less damage to the renal parenchyma than when it is carried out by older methods which involve the insertion of curved forceps through the parenchyma. The postoperative care involves roentgenographic examination to determine the exact position of the tube in the kidney. This is best done by taking one film without injecting any medium and then taking one after moderately filling the pelvis with the desired opaque solution. The tube should not be removed for at least ten days, and if longer drainage is desired the original tube should be left in position; in general, as long as it drains satisfactorily and does not become encrusted.

Uretero-enterostomy may be indicated for a number of conditions, namely, congenital abnormalities, inoperable vesicovaginal fistula, intolerable vesical tuberculosis, intractable interstitial cystitis and cancer of the bladder. In general, the operation should be confined to those patients whose ureters are within approximately normal limits in size. Careful preoperative preparation of the intestinal tract by use of a low residue diet and cleansing enemas is of great importance. The author stated a preference for a two stage operation, with transplantation of one ureter at a time. The loop of sigmoid colon to be utilized is drawn through an incision in the peritoneum. After the completion of the anastomosis, the intestine is fixed to the peritoneum in such a way that the line of suture is extraperitonealized. The chief contraindication to the two stage operation is cancer of the bladder, in which case bilateral uretero-enterostomy may be desirable as a single operation. The portion of the ureter that is mobilized should be that which leads directly from the brim of the pelvis to the point on the intestine selected for anastomosis.

After uretero-enterostomy, the patient should be given fluids plentifully, either subcutaneously or intravenously. A rectal tube is kept

constantly in place for from ten to fourteen days. Nothing is given by mouth for forty-eight hours, and then small amounts of water are given for the next several days, after which a liquid diet, without milk, is administered for a few more days. Enemas are contraindicated for at least ten days. When the patient's condition permits, the status of the kidneys should be determined by intravenous urography.

Cutaneous ureterostomy is almost exclusively reserved for cases in which the ureters are grossly abnormal. Under such circumstances the ureters are dilated and readily permit the introduction of a fairly large sized, soft rubber catheter. The most desirable point for bringing the ureter to the abdominal wall is just medial to the anterosuperior iliac spine. The ureter is exposed and mobilized through an oblique incision, the center of which lies on a line between the anterosuperior iliac spine and the umbilicus. The ureter is freed down into the pelvis for a distance sufficient to permit the lower end of the ureter to be brought into the wound and project beyond the skin for a distance of several centimeters. The ureter should also be freed well above the pelvic brim in such a way that it can be brought out through the incision in a gentle curve without any kinks. The ureter should be brought through the skin obliquely and not at a right angle, as the latter technic will tend to cause too sharp a bend in the ureter just below the abdominal wall. A soft rubber catheter of a size that fits snugly in the lumen of the ureter is inserted into the renal pelvis, and the satisfactory position of the tube is determined by complete aspiration of all the solution that is injected. The catheter is then held in position by two catgut ligatures which are placed one above the other close to the distal end of the ureter. No sutures are placed through the ureter.

Postoperative care in cases in which cutaneous ureterostomy has been performed involves roentgenographic examination to determine definitely the position of the tube in the renal pelvis. After the protruding portion of the ureter has sloughed off, leaving a pouting roset of mucous membrane on the abdominal wall, the catheter is maintained in position by heavy silk ties attached to pieces of adhesive tape placed at right angles to the wound. The renal pelvis is irrigated daily with a bland solution. Subsequently the necessity of irrigating the kidney depends on the amount of infection and dilatation that is present. There is considerable variation in the frequency with which the catheter should be changed. This may vary from several weeks to several months or more. No dogmatic rule can be made. The catheter should be changed with sufficient frequency to maintain complete and adequate drainage and to avoid encrustation of the catheter.

ANURIA

Cubitt [103] reported 2 cases of anuria and discussed the problems relating to this condition, particularly the reflex type, as exemplified by the renorenal or ureterorenal reflex when an obstruction on one side is capable of producing suppression in the contralateral kidney which is otherwise normal.

He said that the unobstructed kidney in cases of reflex anuria is enlarged and deeply congested. This refutes the hypothesis of a reflex vascular spasm or cramp, for the contralateral kidneys should then be small, pale and bloodless.

Recent studies on secretion of urine have disclosed that in the normal unobstructed kidney there is a certain intrarenal pressure acting in all directions within the capsules of the organ and tending to obliterate the tubules, thus offering a constant resistance to the production of urine. Increase of this intrarenal pressure through edema, ureteral obstruction with increased intrapelvic pressure or venous obstruction would result in a diminished output of urine.

It is possible that spasm of one ureter in response to impaction of a stone sets up afferent nervous impulses which, either by direct reflex action or by release of some hormone (epinephrine or posterior pituitary), cause vascular changes in the other kidney, an alteration in capillary permeability and an exudation of fluid into the renal parenchyma; the increased intrarenal pressure obstructs the tubules and raises the pressure of urine, opposing filtration; at the same time it causes partial obstruction to the venous outflow, so that the kidney is congested with blood.

In one of Cubitt's cases spinal anesthesia was used in addition to the administration of dextrose solution intravenously and ureteral catheterization, so that it was impossible to attribute the successful result which was obtained to any one type of treatment separately.

However, spinal anesthesia is put forward as a rational therapeutic measure worthy of trial in cases of reflex anuria. This applies whatever the etiology, since the afferent path at least must be a nervous one.

TRICHOMONAS

Allen [104] stated that vaginitis caused by Trichomonas vaginalis is one of the common gynecological diseases. High dry magnification of the fresh, unstained vaginal secretion under reduced illumination simplifies

103. Cubitt, A. W.: The Problem of Anuria: A Review of Recent Work on Renal Physiology, with Reports of Two Cases, Brit. J. Surg. **24**:215-226 (Oct.) 1936.

104. Allen, Edward: Trichomonas Vaginalis Vaginitis, Am. J. Surg. **33**: 523-528 (Sept.) 1936.

diagnosis. Later staining of the dried secretion will serve to distinguish the other common forms of vaginal infection, such as yeast infection and gonorrhea.

The profuse bubbly discharge which is found in this condition is also laden with various strains of streptococci. These streptococci may invade the urinary tract, Bartholin's glands and probably the deeper structures of the pelvis. In like manner, the urinary tract of the male may become infected during coitus either by the coccoid organisms or by the motile flagellates themselves, and a troublesome urethritis or prostatitis is the result. Constant reinfection of the female renders permanent cure impossible until the focus in the male has been treated.

Permanent cure of vaginitis caused by Trichomonas will depend on recognition of these possible avenues of infection. Elevation of the general resistance of the patient is important in the therapy.

STERILIZATION

Baer [105] stated that sterilization is permissible in any woman in whom pregnancy will aggravate existing disease which is not amenable to direct cure, undo previous corrective gynecological procedures or jeopardize her life. Written consent from both husband and wife should be obtained. Sterilization is urgently desirable in women with certain types of mental disease and congenital defects.

For permanent sterilization by surgical methods, tubal crushing and cornual excision are the simplest and surest of all the available methods. When surgical methods are contraindicated, permanent sterilization can be obtained by either roentgen or radium therapy. This always involves destruction of ovarian function and onset of the menopause.

Temporary sterilization by surgical methods is usually a failure. Irradiation for this purpose is unreliable and fraught with the risk of producing permanent sterilization. Contraception is the logical procedure if pregnancy is to be avoided temporarily.

Combined sterilization and therapeutic abortion are indicated in approximately 13 per cent of cases in which sterilization is necessary. Abdominal hysterotomy by a transverse fundal incision, which includes cornual excision, is the operation of choice.

Biologic methods for the attainment of sterilization are still entirely experimental. The only one that holds any hope in the future is the utilization of spermatoxins.

Hagner [106] stated that the most frequent cause of sterility in the male is inflammatory occlusion of the epididymis or vas deferens. Atrophy

105. Baer, J. L.: Sterilization, Am. J. Surg. **33**:513-517 (Sept.) 1936.

106. Hagner, F. R.: The Operative Treatment of Sterility in the Male, J. A. M. A. **107**:1851-1854 (Dec. 5) 1936.

of the testis rarely occurs in epididymitis, especially in the type associated with gonorrhea. Traumatic epididymitis rarely leads to sterility.

Hagner has never had a successful case after operation for sterility in which the patient has not had a history of bilateral epididymitis. There are two conditions that must be present for a successful result in sterility of this type: 1. The vas must be patulous above the point of anastomosis. 2. The globus major, or the upper portion of the body of the epididymis, must contain live spermatozoa. He has had no successful results except in cases in which silver wire was used as a suture. Hagner only briefly mentioned the steps of the operation, as these have been reported many times already and repetition is unnecessary. It is important to control all bleeding either by torsion or by pressure before the anastomosis is made. He has always done a bilateral operation, being careful not to make the incision in the vas too high up, thus giving a double chance for a cure and, in case of failure the first time, allowing for a subsequent operation.

In the 65 cases Hagner reported 77 operations were performed. In 12 cases a second operation was necessary because of initial failure. Of these 12 patients, 7 were cured by the second operation. Nearly all the operations were done by lateral anastomosis except the few rather atypical ones already mentioned. Sometimes one finds occlusion of the vas at the first incision, and by going further up the vas one is able to get above this obstruction. Unless great care is exercised to cut only into the lumen of the vas, which is recognizable by the yellowish tinge of its lining, there is likelihood of the operator carrying the incision through the entire diameter of the tube. It is important not to strip the vas deferens too close. Hagner places the first suture at the distal end of the incision in the vas, taking a good heavy bite, as this is the anchoring suture for the operation and the obstruction is below this point. The suture is then anchored firmly in the lower end of the elliptic incision of the epididymis. Two lateral sutures are then placed to take a fairly heavy bite in the epididymis and include some of the cut tubules. If only the fibrous covering of the epididymis is taken up in the suture, the cut tubules drop back when the anastomosis is made. The suture is then passed through the cut edges of the vas, just enough tissue being taken to approximate the edges. The last suture is passed in the same way through the upper end of the incision in the epididymis. It is then passed through the vas, at the upper angle of the incision, being carefully placed so as not to occlude the lumen. Hagner tests this out with a tear duct probe. The anastomosis is then complete. The instruments that he uses are iridectomy knives, scissors and artery forceps, such as those commonly used in operations on the eye.

Hagner stated that the operation, while tedious, is not dangerous to life. He always uses general anesthesia. He stated that in order to avoid the formation of scar tissue local infiltration should not be used. The operation cannot compromise the function of an organ that has already proved functionless. In no class of cures will the surgeon be rewarded by his patients with a greater warmth of gratitude.

REJUVENATION

Blum,[107] after discussion of the philosophic and physiologic aspects of old age and rejuvenation, took up the different types of operations and treatments for rejuvenation that have been put forth in the last years, since the first publication of Steinach in 1920. These included Steinach's operations and modifications, sympathicodiaphtheresis, transplantation of sexual glands and nonoperative treatment, such as diathermy, roentgen therapy, hormonal therapy and psychotherapy. Blum confined his paper to rejuvenation in the male.

Steinach's theory can be reviewed briefly as follows: The testis is composed of two parts, the spermatogenic and the hormonal. Old age is attributable to atrophy of the hormonal part of the testis. By ligation of the vas deferens, sperms are kept back, the spermatogenic epithelial cells atrophy by pressure, and the interstitial cells, the carriers of the hormonal production, hypertrophy.

Blum has used vasoligation in many hundred cases, mostly in patients suffering from prostatic obstruction. He has never been able to find any lasting rejuvenating effect that could not be attributed to other causes (relief of symptoms by relief of prostatic obstruction, etc.). Extensive experiments on animals (Romeis, 1933) never demonstrated any hypertrophy of the interstitial cells after vasoligation, so that Steinach's theory lacks real proof. The same is true for all modifications of Steinach's first described operation.

Not much better founded is Doppler's operation, which consists in a chemical sympathectomy of the blood vessels to the testis. By that means the blood flow to the testis is increased, but the effect wears off much too soon. Better results are obtainable from the transplantation of testes and, without any operation, from the injection of hormonal substances, especially androgen. The underlying thought in all treatments for rejuvenation, or as Blum would prefer to call it, reactivation and regeneration, is an increased circulation of hormones in the organism. It is essential that the hormones find an organism which is still able and ready to react to them. This increase of hormones can

107. Blum, Viktor: Verjüngung und Verjüngungsoperationen, Wien. med. Wchnschr. **86**:989-994 (Sept. 5) 1936.

be reached by injection or by activation of endocrine glands by treatment with diathermy, roentgen rays and ultraviolet light. Those measures should be tried out first, and operation, with its short effect, performed only in exceptional cases.

UROGRAPHY

Osterberg [108] was prompted to describe the opaque medium used by the Section on Urology at the Mayo Clinic for the purpose of retrograde pyelography because of frequent inquiry as to its composition and preparation. This medium has been used for several years and has been satisfactory.

It is prepared as follows:

Hippuran crystals, 160 Gm., are dissolved in 200 cc. of commercially prepared solution which contains metaphen, 1:2,500. This quantity is increased to 800 cc. by the addition of a solution of 6 per cent acacia and 1 per cent sodium chloride. This 6 per cent solution of acacia is the same as that used for intravenous purposes. Addition of acacia results in precipitation of a small amount of hippuran. This precipitate is filtered off on a Buchner funnel, and the clear solution is placed in 15 cc. cotton-stoppered tubes. These are autoclaved, and the medium is ready for use. If difficulty is encountered in obtaining a clear solution, filtration through a pad of infusorial earth may be resorted to. The resulting solution contains approximately 20 per cent hippuran, 4 per cent acacia and metaphen, 1:10,000, to insure self-sterilization.

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108. Osterberg, A. E.: Preparation of Medium for Retrograde Pyelography, Proc. Staff Meet., Mayo Clin. **11**:560 (Aug. 26) 1936.